Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	WO199817299	US-PGPUB; USPAT; DERWENT	ADJ	ON	2006/01/09 10:53
L2	1	WO "9817299"	US-PGPUB; USPAT; DERWENT	ADJ	ON	2006/01/09 11:16
L3	5	"6521815"	US-PGPUB; USPAT; DERWENT	ADJ	ON	2006/01/09 11:52
L4	0	rack fusion	US-PGPUB; USPAT; DERWENT	ADJ	ON	2006/01/09 11:52
L5	0	rack tat	US-PGPUB; USPAT; DERWENT	ADJ	ON	2006/01/09 11:52
L6	11	rack tat	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/01/09 11:54
L7	0	rack arginine	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/01/09 11:54
L8	0	rack polyarg	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/01/09 11:55
L9	0	rack polyarginine	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/01/09 11:55
L10	900	rack fus$	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/01/09 11:55
L11	141	rack fusion	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/01/09 11:55
L12	214	rack fused	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/01/09 11:55

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? b5, 155
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     $0.00  Estimated cost File410
     $0.02  TELNET
     $0.02  Estimated cost this search
     $0.02  Estimated total session cost   0.318 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R) 1969-2006/Jan W1
         (c) 2006 BIOSIS
  File 155:MEDLINE(R) 1951-2006/Dec 12
         (c) format only 2006 Dialog
*File 155: MEDLINE has ceased updating with UD=20051212, until futher
notice, as processing is being done to the file.

      Set  Items  Description
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Set     Items   Description
S1          5   RACK AND FUSION
S2          9   RACK AND TAT
S3          6   RD  (unique items)
S4          2   RACK AND POLYARG?
S5          1   RD  (unique items)
S6         85   RACK AND TRANSPORT?
S7         80   RD  (unique items)
S8         18   S7 AND RECEPTOR
S9        315   E4-E11
S10       207   RD  (unique items)
S11        94   S10 AND TRANSPORT
S12        32   S10 AND RACK
S13        19   S12 AND TRANSPORT?
? t s1/7/1-5

 1/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0015629592   BIOSIS NO.: 200510324092
The interaction of RACK1 with KB-Ras
AUTHOR: Chuang Nin-Nin (Reprint); Chen Jia-Lin
AUTHOR ADDRESS: Acad Sinica, Inst Zool, Taipei 11529, Taiwan**Taiwan
JOURNAL: FASEB Journal  19 (4, Suppl. S, Part 1): pA508 MAR 4 2005 2005
CONFERENCE/MEETING: Experimental Biology 2005 Meeting/35th International
Congress of Physiological Sciences  San Diego, CA, USA  March 31 -April 06,
2005; 20050331
SPONSOR: Amer Assoc Anatomists
         Amer Assoc Immunologists
         Amer Physiol Soc
         Amer Soc Biochem & Mol Biol
         Amer Soc Investigat Pathol
         Amer Soc Nutr Sci
         Amer Soc Pharmacol & Expt Therapeut
         Int Union Physiol Sci
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: %%%RACK%%%) protein was purified from human placenta with an
  affinity column HiTrap-PEPTaxol (PEp(Taxol)) constructed from
  beta-tubulin peptide specific for Taxol binding. The isolated RACK1
  protein was phosphorylated byc-Src tyrosine kinase with limited amounts.
  In contrast, after the treatment with alkaline phosphatase, the RACK1 of
  human placenta was significantly phosphorylated by c-Src as revealed on
  the autoradiogram. The purified placental RACK1 exhibited high affinity
  for GTP-locked K-B-Ras mutant proteins without any concern whether RACK1
  was phosphorylated by c-Src or not. The interaction between RACK1 and
  GTP-locked K-B-Ras mutant proteins was confirmed with mouse-encoded RACK1
  %%%fusion%%% proteins. The selective affinity betweenGTP-locked KB-Ras
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mutant proteins and RACK1 protein was sufficient to interrupt the binding of RACK1 with beta-tubulin (as revealed by the PEPTaxol sequence). Of interests, KB-Ras in the GDP bound form (not in the GTP bound form) was shown to share the same binding site for RACK1 protein and Taxol on P-tubulin, but with less affinity for P-tubulin than RACK1. Thus, the selective reaction of K-B-Ras mutant proteins in the GDP bound form with PEpT-1 and the strong affinity of KB-Ras mutant proteins in the GTP bound form with RACK1 might operate a feed back mechanism to limit the ratio of GTP-boundto GDP-bound Ras in the cytosol and to deprive RACK1 from cytoskeleton as well as to switch off PKC signaling.

1/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015329644 BIOSIS NO.: 200510024144
Protocols for production of selenomethionine-labeled proteins in 2-L polyethylene terephthalate bottles using auto-induction medium
AUTHOR: Sreenath Hassan K (Reprint); Bingman Craig A; Buchan Blake W; Seder Kory D; Burns Brendan T; Geetha Holalkere V; Jeon Won Bae; Vojtik Frank C ; Aceti David J; Frederick Ronnie O; Phillips George N; Fox Brian G
AUTHOR ADDRESS: Univ Wisconsin, Dept Biochem, Ctr Eukaryot Struct Genom, 433 Babcock Dr, Madison, WI 53706 USA**USA
AUTHOR E-MAIL ADDRESS: sreenath@biochem.wisc.edu; bgfox@biochem.wisc.edu
JOURNAL: Protein Expression and Purification 40 (2): p256-267 APR 05 2005
ISSN: 1046-5928
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protocols have been developed and applied in the high-throughput production of selenomethionine labeled %%%fusion%%% proteins using the conditional Met auxotroph Escherichia coli B834. The larp-scale growth and expression uses a chemically defined auto-induction medium containing 125 mg L-1 selenomethionine, salts and trace metals, other amino acids including 10 mg L-1 of methionine, vitamins except vitamin B-12, and glucose, glycerol, and alpha-lactose. A schematic for a shaker %%%rack%%% that can hold up to twenty-four 2-L polyethylene terephthalate beverage bottles in a standard laboratory refrigerated floor shaker is provided. The growth cycle from inoculation of the culture bottle through the growth, induction, and expression was timed to take similar to 24 h. Culture growth in the autoinduction medium gave an average final optical density at 600 nm of similar to 6 and an average wet cell mass yield of similar to 14 g from 2 L of culture in greater than 150 expression trials. A simple method for visual scoring of denaturing electrophoresis gels for total protein expression, solubility, and effectiveness of %%%fusion%%% protein proteolysis was developed and applied. For the favorably scored expression trials, the average yield of purified, selenomethionine-labeled target protein obtained after proteolysis of the %%%fusion%%% protein was similar to 30 mg. Analysis by mass spectrometry showed greater than 90% incorporation of selenomethionine over a similar to 8-fold range of selenomethionine concentrations in the growth medium, with higher growth rates observed at the lower selenomethionine concentrations. These protein preparations have been utilized to solve X-ray crystal structures by multiwavelength anomalous diffraction phasing. (c) 2005 Elsevier Inc. All rights reserved.

1/7/3 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

18049728 PMID: 15766867
Protocols for production of selenomethionine-labeled proteins in 2-L polyethylene terephthalate bottles using auto-induction medium.
Sreenath Hassan K; Bingman Craig A; Buchan Blake W; Seder Kory D; Burns Brendan T; Geetha Holalkere V; Jeon Won Bae; Vojtik Frank C; Aceti David J; Frederick Ronnie O; Phillips George N; Fox Brian G
Department of Biochemistry, Center for Eukaryotic Structural Genomics, University of Wisconsin-Madison, 433 Babcock Drive, Madison, WI 53706-1549,

USA. sreenath@biochem.wisc.edu
Protein expression and purification (United States) Apr 2005, 40 (2) p256-67, ISSN 1046-5928 Journal Code: 9101496
Contract/Grant No.: P50 GM-64598; GM; NIGMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Protocols have been developed and applied in the high-throughput production of selenomethionine labeled %%%fusion%%% proteins using the conditional Met auxotroph Escherichia coli B834. The large-scale growth and expression uses a chemically defined auto-induction medium containing 125 mg L(-1) selenomethionine, salts and trace metals, other amino acids including 10 mg L(-1) of methionine, vitamins except vitamin B12, and glucose, glycerol, and alpha-lactose. A schematic for a shaker %%%rack%%% that can hold up to twenty-four 2-L polyethylene terephthalate beverage bottles in a standard laboratory refrigerated floor shaker is provided. The growth cycle from inoculation of the culture bottle through the growth, induction, and expression was timed to take approximately 24 h. Culture growth in the auto-induction medium gave an average final optical density at 600 nm of approximately 6 and an average wet cell mass yield of approximately 14 g from 2 L of culture in greater than 150 expression trials. A simple method for visual scoring of denaturing electrophoresis gels for total protein expression, solubility, and effectiveness of %%%fusion%%% protein proteolysis was developed and applied. For the favorably scored expression trials, the average yield of purified, selenomethionine-labeled target protein obtained after proteolysis of the %%%fusion%%% protein was approximately 30 mg. Analysis by mass spectrometry showed greater than 90% incorporation of selenomethionine over a approximately 8-fold range of selenomethionine concentrations in the growth medium, with higher growth rates observed at the lower selenomethionine concentrations. These protein preparations have been utilized to solve X-ray crystal structures by multiwavelength anomalous diffraction phasing.

Record Date Created: 20050315
Record Date Completed: 20050630

1/7/4 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13077497 PMID: 11046044

Receptor for activated C-kinase (%%%RACK%%%-1), a WD motif-containing protein, specifically associates with the human type I IFN receptor.

Croze E; Usacheva A; Asarnow D; Minshall R D; Perez H D; Colamonici O
Department of Immunology, Berlex Biosciences, Richmond CA 94804, USA. ed croze@berlex.com

Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Nov 1 2000, 165 (9) p5127-32, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: CA55079; CA; NCI; GM54709; GM; NIGMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The cytoplasmic domain of the human type I IFN receptor chain 2 (IFNAR2c or IFN-alphaRbetaL) was used as bait in a yeast two-hybrid system to identify novel proteins interacting with this region of the receptor. We report here a specific interaction between the cytoplasmic domain of IFN-alphaRbetaL and a previously identified protein, %%%RACK%%%-1 (receptor for activated C kinase). Using GST %%%fusion%%% proteins encoding different regions of the cytoplasmic domain of IFN-alphaRbetaL, the minimum site for %%%RACK%%%-1 binding was mapped to aa 300-346. %%%RACK%%%-1 binding to IFN-alphaRbetaL did not require the first 91 aa of %%%RACK%%%-1, which includes two WD domains, WD1 and WD2. The interaction between %%%RACK%%%-1 and IFN-alphaRbetaL, but not the human IFN receptor chain 1 (IFNAR1 or IFN-alphaRalpha), was also detected in human Daudi cells by coimmunoprecipitation. %%%RACK%%% -1 was shown to be constitutively associated with IFN-alphaRbetaL, and this association was not effected by stimulation of Daudi cells with type I IFNs (IFN-betalb). %%%RACK%%%-1

itself did not become tyrosine phosphorylated upon stimulation of Daudi cells with IFN-beta1b. However, stimulation of cells with either IFN-beta1b or PMA did result in an increase in detectable immunofluorescence and intracellular redistribution of %%%RACK%%%-1.
Record Date Created: 20001103
Record Date Completed: 20001130

1/7/5 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09906667 PMID: 1326322
p65 fragments, homologous to the C2 region of protein kinase C, bind to the intracellular receptors for protein kinase C.
Mochly-Rosen D; Miller K G; Scheller R H; Khaner H; Lopez J; Smith B L
Department of Neurology, Ernest Gallo Clinic and Research Center, University of California, San Francisco 94110.
Biochemistry (UNITED STATES) Sep 8 1992, 31 (35) p8120-4, ISSN 0006-2960 Journal Code: 0370623
Contract/Grant No.: AA08353; AA; NIAAA; HL08406; HL; NHLBI; HL43380; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Receptors for activated protein kinase C (RACKs) have been isolated from the particulate cell fraction of heart and brain. We previously demonstrated that binding of protein kinase C (PKC) to RACKs requires PKC activators and is via a site on PKC that is distinct from the substrate binding site. Here, we examine the possibility that the C2 region in the regulatory domain of PKC is involved in binding of PKC to RACKs. The synaptic vesicle-specific p65 protein contains two regions homologous to the C2 region of PKC. We found that three p65 fragments, containing either one or two of these PKC C2 homologous regions, bound to highly purified RACKs. Binding of the p65 fragments and PKC to RACKs was mutually exclusive; preincubation of RACKs with the p65 fragments inhibited PKC binding, and preincubation of RACKs with PKC inhibited binding of the p65 fragments. Preincubation of the p65 fragments with a peptide resembling the PKC binding site on RACKs also inhibited p65 binding to RACKs, suggesting that PKC and p65 bind to the same or nearby regions on RACKs. Since the only homologous region between PKC and the p65 fragments is the C2 region, these results suggest that the C2 region on PKC contains at least part of the %%%RACK%%% binding site.
Record Date Created: 19921016
Record Date Completed: 19921016
? s rack and tat
1075 RACK
14148 TAT
S2 9 RACK AND TAT
? rd
S3 6 RD (unique items)
? t s3/7/1-6

3/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015621854 BIOSIS NO.: 200510316354
Activated E-protein kinase C accelerates the transition from compensatory left ventricular hypertrophy to heart failure in hypertensive rats
AUTHOR: Inagaki Koichi (Reprint); Begley Rebecca; Mochly-Rosen Daria
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94305 USA**USA
JOURNAL: Circulation 110 (17, Suppl. S): p598 OCT 26 2004 2004
CONFERENCE/MEETING: 77th Scientific Meeting of the American-Heart-Association New Orleans, LA, USA November 07 -10, 2004; 20041107
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: We have previously demonstrated that epsilon protein kinase C (epsilon PKC) levels are increased in compensatory hypertrophied left ventricle (LV) in Dahl salt-sensitive rats with systemic hypertension, and the activation of epsilon PKC induces the physiological LV hypertrophy without impaired cardiac function in transgenic mice expressing the epsilon PKC selective activator peptice (Psi epsilon %%%RACK%%%). Hypothesis: Here, we hypothesized that epsilon PKC signaling is necessary to maintain compensatory hypertrophy and thus the treatment with IVERACK should prevents the progression of heart failure. Methods: Dahl salt-sensitive rats were fed with 8% salt diet from 6 weeks old to induce systemic hypertension. Dahl salt-sensitive rats were treated continuously with Psi epsilon %%%RACK%%% (n=15) or with control carrier peptice %%%Tat%%% (n=12) from 15 to 17 weeks old using subcutaneously implanted osmotic pump. Cardiac function was determined by echocardiography. Results: The treatment with Psi epsilon %%%RACK%%% before the transition to heart failure shortened the survival rate (Psi epsilon %%%RACK%%% 118.9 +/- 2.8 vs. control 138.5 +/- 10.3 days old, P<0.05). In addition, the treatment with Psi epsilon %%%RACK%%% resulted in reduced fractional shortening (Psi epsilon %%%RACK%%% 35.9 +/- 3.3 vs. control 46.5 +/- 2.6 %, P<0.05), increased LV end diastolic dimension (Psi epsilon %%%RACK%%% 8.3 +/- 0.4 vs. control 7.5 +/- 0.2 mm, P<0.05), increased systolic wall stress (Psi epsilon %%%RACK%%% 139.0 +/- 25.4 vs. control 85.3 +/- 7.2 g/cm(2), P<0.05), and increased LV weight (Psi epsilon %%%RACK%%% 1.38 +/- 0.05 vs. control 1.22 +/- 0.04 g, P<0.05) and lung weight (Psi epsilon %%%RACK%%% 3.28 +/- 0.98 vs. control 1.73 +/- 0.1 g, P<0.05) as compared with the treatment with the control peptice at 17 weeks old. There were no significant differences between the two groups in systolic blood pressure (Psi epsilon %%%RACK%%% 255.2 +/- 7.9 vs. control 247.9 +/- 4.7 mmHg) and in body weight (Psi epsilon %%%RACK%%% 345.4 +/- 16.4 vs. control 354.2 +/- 13.0 g). Conclusion: Continuous activation of epsilon PKC in hypertrophied LV myocardium of hypertensive rats induces further myocardial hypertrophy, but accelerates the transition to heart failure in contrast to our initial hypothesis.

3/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014469191 BIOSIS NO.: 200300424035
Additive protection of the ischemic heart ex vivo by combined treatment with delta-protein kinase C inhibitor and epsilon-protein kinase C activator.
AUTHOR: Inagaki Koichi; Hahn Harvey S; Dorn Gerald W; Mochly-Rosen Daria (Reprint)
AUTHOR ADDRESS: Department of Molecular Pharmacology, Stanford University School of Medicine, 269 Campus Dr, CCSR, Room 3145A, Stanford, CA, 94305-5174, USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Circulation 108 (7): p869-875 August 19, 2003 2003
MEDIUM: print
ISSN: 0009-7322 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Protein kinase C (PKC) plays a major role in cardioprotection from ischemia/reperfusion injury. Using an HIV-1 %%%Tat%%% protein-derived peptide to mediate rapid and efficient transmembrane delivery of peptide regulators of PKC translocation and function, we examined the cardioprotective effect of selective delta-PKC inhibitor (deltaV1-1) and epsilon-PKC activator (psiepsilonRACK) peptides for ischemia/reperfusion damage in isolated perfused rat hearts. Furthermore, we examined the protective effects of these PKC isozymes in isolated perfused hearts subjected to ischemia/reperfusion damage using transgenic mice expressing these peptides specifically in their cardiomyocytes. Methods and Results: In isolated perfused rat hearts, administration of deltaV1-1 but not psiepsilonRACK during reperfusion

improved cardiac function and decreased creatine phosphokinase release. In contrast, pretreatment with psiepsilonRACK but not deltaV1-1, followed by a 10-minute washout before ischemia/reperfusion, also improved cardiac function and decreased creatine phosphokinase release. Furthermore, administration of psiepsilonRACK before ischemia followed by deltaV1-1 during reperfusion only conferred greater cardioprotective effects than that obtained by each peptide treatment alone. Both the delta-PKC inhibitor and epsilon-PKC activator conferred cardioprotection against ischemia/reperfusion injury in transgenic mice expressing these peptides in the heart, and coexpression of both peptides conferred greater cardioprotective effects than that obtained by the expression of each peptide alone. Conclusions: delta-PKC inhibitor prevents reperfusion injury, and epsilon-PKC activator mimics ischemic preconditioning. Furthermore, treatment with both peptides confers additive cardioprotective effects. Therefore, these peptides mediate cardioprotection by regulating ischemia/reperfusion damage at distinct time points.

3/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013837006 BIOSIS NO.: 200200430517
Ethanol induces gene expression via nuclear compartmentalization of receptor for activated C kinase 1
AUTHOR: He Dao-Yao; Vagts Alicia J; Yaka Rami; Ron Dorit (Reprint)
AUTHOR ADDRESS: 5858 Horton St., Suite 200, Emeryville, CA, 94608, USA**USA
JOURNAL: Molecular Pharmacology 62 (2): p272-280 August, 2002 2002
MEDIUM: print
ISSN: 0026-895X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Scaffolding proteins such as receptor for activated C kinase (%%%RACK%%%) 1 are involved in the targeting of signaling proteins and play an important role in the regulation of signal transduction cascades. Recently, we found that in cultured cells and in vivo, acute ethanol exposure induces the nuclear compartmentalization of RACK1. To elucidate a physiological role for nuclear RACK1, the %%%Tat%%% protein transduction system was used to transduce RACK1 and RACK1-derived fragments into C6 glioma cells. We found that nuclear RACK1 is mediating the induction of the immediate early gene c-fos expression induced by ethanol. First, transduction of full-length RACK1 (%%%Tat%%%-RACK1) resulted in the induction of c-fos expression and enhancement of ethanol activities. Second, we determined that the C terminus of RACK1 (%%%Tat%%% -RACK1DELTAN) is mediating transcription. Third, we identified a dominant negative fragment of RACK1 that inhibited the nuclear compartmentalization of endogenous RACK1 and inhibited ethanol-induction of c-fos mRNA and protein expression. Last, acute exposure to ethanol or transduction of full-length %%%Tat%%%-RACK1 resulted in an increase in mRNA levels of an activator protein 1 site-containing gene, PAC1 (pituitary adenylate cyclase-activating polypeptide receptor type 1), suggesting that nuclear RACK1 is involved in the regulation of the expression of genes that are altered upon acute ethanol treatment. These results may therefore have important implications for the study of alcohol addiction.

3/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013600152 BIOSIS NO.: 200200193663
Molecular transporters for peptides: Delivery of a cardioprotective epsilonPKC agonist peptide into cells and intact ischemic heart using a transport system, R7
AUTHOR: Chen Leon; Wright Lee R; Chen Che-Hong; Oliver Steven F; Wender Paul A (Reprint); Mochly-Rosen Daria
AUTHOR ADDRESS: Department of Chemistry, Stanford University, Stanford, CA,

94305, USA**USA
JOURNAL: Chemistry and Biology (London) 8 (12): p1123-1129 December, 2001 2001
MEDIUM: print
ISSN: 1074-5521
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Recently, we reported a novel oligoguanidine transporter system, polyarginine (R7), which, when conjugated to spectroscopic probes (e.g., fluorescein) and drugs (e.g., cyclosporin A), results in highly water-soluble conjugates that rapidly enter cells and tissues. We report herein the preparation of the first R7 peptide conjugates and a study of their cellular and organ uptake and functional activity. The octapeptide psiepsilonRACK was selected for this study as it is known to exhibit selective epsilon protein kinase C isozyme agonist activity and to reduce ischemia-induced damage in cardiomyocytes. However, psiepsilonRACK is not cell-permeable. Results: Here we show that an R7-psiepsilonRACK conjugate readily enters cardiomyocytes, significantly outperforming psiepsilonRACK conjugates of the transporters derived from HIV %%%Tat%%% and from Antennapedia. Moreover, R7-psiepsilonRACK conjugate reduced ischemic damage when delivered into intact hearts either prior to or after the ischemic insult. Conclusions: Our data suggest that R7 converts a peptide lead into a potential therapeutic agent for the ischemic heart.

3/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012930352 BIOSIS NO.: 200100102191
Novel in vivo delivery of a peptide agonist epsilonprotein kinase C induces acute protection against reperfusion injury in mouse heart
AUTHOR: Gray Mary O (Reprint); Zhou Hui-Zhong (Reprint); Karliner Joel S (Reprint)
AUTHOR ADDRESS: VA Medical Ctr, CVRI, Univ of CA, San Francisco, CA, USA** USA
JOURNAL: Circulation 102 (18 Supplement): pII.85 October 31, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: Abstracts from American Heart Association Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000; 20001112
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

3/7/6 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

18064770 PMID: 15611364
Cardioprotection by epsilon-protein kinase C activation from ischemia: continuous delivery and antiarrhythmic effect of an epsilon-protein kinase C-activating peptide.
Inagaki Koichi; Begley Rebecca; Ikeno Fumiaki; Mochly-Rosen Daria
Department of Molecular Pharmacology, Stanford University School of Medicine, Stanford, Calif 94305-5174, USA.
Circulation (United States) Jan 4 2005, 111 (1) p44-50, ISSN 1524-4539 Journal Code: 0147763
Contract/Grant No.: HL-52141; HL; NHLBI
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: We previously showed that a selective activator peptide of epsilon-protein kinase C (PKC), psi(epsilon)%%%RACK%%% , conferred

cardioprotection against ischemia-reperfusion when delivered ex vivo before the ischemic event. Here, we tested whether in vivo continuous systemic delivery of psi(epsilon)%%%RACK%%% confers sustained cardioprotection against ischemia-reperfusion in isolated mouse hearts and whether psi(epsilon)%%%RACK%%% treatment reduces infarct size or lethal arrhythmias in porcine hearts in vivo. METHODS AND RESULTS: After psi(epsilon) %%%RACK%%% was systemically administered in mice either acutely or continuously, hearts were subjected to ischemia-reperfusion in an isolated perfused model. Whereas psi(epsilon)%%%RACK%%% -induced cardioprotection lasted 1 hour after a single intraperitoneal injection, continuous treatment with psi(epsilon)%%%RACK%%% induced a sustained preconditioned state during the 10 days of delivery. There was no desensitization to the therapeutic effect, no downregulation of epsilonPKC, and no adverse effects after sustained psi(epsilon)%%%RACK%%% delivery. Porcine hearts were subjected to ischemia-reperfusion in vivo, and psi(epsilon)%%%RACK%%% was administered by intracoronary injection during the first 10 minutes of ischemia. psi(epsilon)%%%RACK%%% treatment reduced infarct size (34+/-2% versus 14+/-1%, control versus psi(epsilon)%%%RACK%%%) and resulted in fewer cases of ventricular fibrillation during ischemia-reperfusion (87.5% versus 50%, control versus psi(epsilon)%%%RACK%%%). CONCLUSIONS: The epsilonPKC activator psi(epsilon)%%%RACK%%% induced cardioprotection both in vivo and ex vivo, reduced the incidence of lethal arrhythmia during ischemia-reperfusion, and did not cause desensitization or downregulation of epsilonPKC after sustained delivery. Thus, psi(epsilon)%%%RACK%%% may be useful for patients with ischemic heart disease. In addition, the psi(epsilon)%%%RACK%%% peptide should be a useful pharmacological agent for animal studies in which systemic and sustained modulation of epsilonPKC in vivo is needed.
  Record Date Created: 20050104
  Record Date Completed: 20050627
  Date of Electronic Publication: 20041220
? s rack and polyarg?
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      S5   1 RD (unique items)
? t s5/7/1

 5/7/1   (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2006 BIOSIS. All rts. reserv.

0013600152   BIOSIS NO.: 200200193663
Molecular transporters for peptides: Delivery of a cardioprotective epsilonPKC agonist peptide into cells and intact ischemic heart using a transport system, R7
AUTHOR: Chen Leon; Wright Lee R; Chen Che-Hong; Oliver Steven F; Wender Paul A (Reprint); Mochly-Rosen Daria
AUTHOR ADDRESS: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA**USA
JOURNAL: Chemistry and Biology (London) 8 (12): p1123-1129 December, 2001
2001
MEDIUM: print
ISSN: 1074-5521
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Recently, we reported a novel oligoguanidine transporter system, polyarginine (R7), which, when conjugated to spectroscopic probes (e.g., fluorescein) and drugs (e.g., cyclosporin A), results in highly water-soluble conjugates that rapidly enter cells and tissues. We report herein the preparation of the first R7 peptide conjugates and a study of their cellular and organ uptake and functional activity. The octapeptide psiepsilonRACK was selected for this study as it is known to exhibit selective epsilon protein kinase C isozyme agonist activity and to reduce ischemia-induced damage in cardiomyocytes. However, psiepsilonRACK is not cell-permeable. Results: Here we show that an R7-psiepsilonRACK conjugate readily enters cardiomyocytes, significantly outperforming psiepsilonRACK conjugates of the transporters

derived from HIV Tat and from Antennapedia. Moreover, R7-psiepsilonRACK conjugate reduced ischemic damage when delivered into intact hearts either prior to or after the ischemic insult. Conclusions: Our data suggest that R7 converts a peptide lead into a potential therapeutic agent for the ischemic heart.

? t s8/7/1-18

8/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015575655 BIOSIS NO.: 200510270155
Janus kinases interact with and phosphorylate %%%Rack%%%-1 (%%%Receptor%%% for activated C kinase-1), a WD motif containing protein.
AUTHOR: Haro Takashi (Reprint); Shimoda Kazuya; Kakumitsu Haruko; Kamezaki Kenjirou; Numata Atsuhiko; Harada Mine
AUTHOR ADDRESS: Kyushu Univ, Dept Internal Med 1, Fukuoka 812, Japan**Japan
JOURNAL: Blood 104 (11, Part 1): p600A NOV 16 2004 2004
CONFERENCE/MEETING: 46th Annual Meeting of the American-Society-of-Hematology San Diego, CA, USA December 04 -07, 2004; 20041204
SPONSOR: Amer Soc Hematol
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We recently reported that Tyk2 was essential for IFN-a-induced B lymphocyte growth inhibition, although Stall is not required for this IFN-a-mediated inhibition. This means that other signaling molecules besides Stat1, and which are activated by Tyk2, are thought to transduce the IFN-a signal inhibiting B lymphocyte growth. We performed a yeast two-hybrid screen for proteins that interact with Tyk2, and identified %%%Rack%%%-L originally described as a %%%receptor%%% for activated C kinase beta, associated with Tyk2. %%%Receptor%%% for activated C kinase (%%%Rack%%%)-1 is a protein kinase C interacting protein, and contains a WD repeat but has no enzymatic activity. In addition to protein kinase C. %%%Rack%%%-1 also binds to Ste, phospholipase C gamma, and ras-GTPase-activating proteins. Thus, %%%Rack%%%-1 is thought to function as a scaffold protein that recruits specific signaling elements. In a cytokine signaling cascade, %%%Rack%%%-1 has been reported to interact with the IFN-alpha/beta %%%receptor%%% and Stat1. In addition, we show here thatRack-1 associates with a member of Jak, tyrosine kinase 2 (Tyk2). Rack1 interacts weakly with the kinase domain and interacts strongly with the pseudo-kinase domain of Tyk2. %%%Rack%%%-1 associates with Tyk2 via two regions, one in the N-terminus and one in the middle portion (a.a. 138-203) of %%%Rack%%%-1. In addition, not only Tyk2 but other Jak kinases associate with %%%Rack%%%-L and each Jak activation causes the phosphorylation of Tyrosine 194 on %%%Rack%%%-1. After phosphorylation, %%%Rack%%%-1 is translocated from cytoplasm or membrane toward the perinuclear region. In addition to functioning as a scaffolding protein, these results raise the possibility that %%%Rack%%% -1 functions as a signaling molecule in cytokine signaling cascades.

8/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015544562 BIOSIS NO.: 200510239062
delta PKC-mediated activation of epsilon PKC in ethanol-induced cardiac protection from ischemia
AUTHOR: Inagaki K; Mochly-Rosen D (Reprint)
AUTHOR ADDRESS: Stanford Univ, Sch Med, Dept Mol Pharmacol, CCSR, Room 3145A,269 Campus Dr, Stanford, CA 94305 USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Journal of Molecular and Cellular Cardiology 39 (2): p203-211 AUG 2005 2005
ISSN: 0022-2828

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous studies have demonstrated that acute ethanol exposure induces activation of 6 protein kinase C (delta PKC) and epsilon PKC, and mimics ischemic preconditioning via epsilon PKC activation. However, the role of delta PKC isozyme in ischemia and reperfusion is still controversial. Here, we investigated the role of delta PKC in ethanol-induced cardioprotection using a selective delta PKC activator (psi delta %%%RACK%%%), or inhibitor (delta V1-1), and a selective epsilon PKC inhibitor (epsilon V1-2) in isolated mouse hearts. Mice were injected intraperitoneally or by gavage with ethanol, regulators of 6 and epsilon PKC or an adenosine A, %%%receptor%%% blocker (DPCPX). Isolated perfused mouse hearts were subjected to a 30-min global ischemia and a 120-min reperfusion, ex vivo. Injection of 0.5 g/kg ethanol 1 h, but not 10 min, before ischemia reduced infarct size and CPK release. Pretreatment with epsilon V1-2 abolished this ethanol-induced cardioprotection. Pretreatment with delta V1-1 induced cardioprotection when injected with ethanol (0.5 g/kg) 10 min before ischemia, but delta V1-1 partly inhibited ethanol-induced cardioprotection when injected with ethanol 1-h before the onset of ischemia. psi delta %%%RACK%%% injection 1 h, but not 10 min, before ischemia induced cardioprotection and translocation of epsilon PKC from the cytosol to the particulate fraction. Pretreatment with DPCPX or epsilon V1-2 inhibited psi delta %%%RACK%%%-induced cardioprotection and translocation of epsilon PKC. Therefore, activation of epsilon PKC-induced by ethanol or by the delta PKC activator is cardioprotective, provided that sufficient time passes to allow delta PKC-induced activation of epsilon PKC, an A(1) adenosine %%%receptor%%%-dependent process. (c) 2005 Published by Elsevier Ltd.

8/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015038855 BIOSIS NO.: 200400409644
Interaction of Gbetagamma with RACK1 and other WD40 repeat proteins
AUTHOR: Chen Songhai (Reprint); Spiegelberg Bryan D; Lin Fang; Dell Edward J; Hamm Heidi E
AUTHOR ADDRESS: Ctr MedDept Pharmacol, Vanderbilt Univ, Room 442,Robinson Res Bldg, Nashville, TN, 37232, USA**USA
AUTHOR E-MAIL ADDRESS: Songhai.Chen@Vanderbilt.edu; Heidi.Hamm@Vanderbilt.edu
JOURNAL: Journal of Molecular and Cellular Cardiology 37 (2): p399-406 August 2004 2004
MEDIUM: print
ISSN: 0022-2828 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Heterotrimeric G-proteins, composed of Galpha and Gbetagamma subunits, transmit numerous and diverse extracellular stimuli via a large family of heptahelical cell-surface receptors to various intracellular effector molecules. The Gbetagamma subunit plays a central role in G-protein signaling. The GP subunit belongs to a large family of WD40 repeat proteins, which adopt a circular beta-bladed propeller structure. This unique structural feature confers interactions of Gbetagamma with a variety of proteins to play diverse functions. Intriguingly, we recently found that Gbetagamma can interact with three other WD40 repeat proteins, %%%receptor%%% for activated C kinase 1 (%%%RACK%%% 1), dynein intermediate chain-1A and a protein of unknown function. This raises the following questions: are interactions among WD40 proteins a common theme and does the formation of a WD40-WD40 repeat protein complex constitute a protein scaffold for integrating signals from different cellular processes. We are beginning to address these issues by studying the interaction between Gbetagamma and %%%RACK%%% 1. Here we will describe the molecular mechanism underlying this interaction and the implications of the interaction on the signal transduction of G-protein and RACK1. Copyright 2004 Published by Elsevier Ltd.

8/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014924167 BIOSIS NO.: 200400294924
Syntaxin 1A and %%%receptor%%% for activated C kinase interact with the N-terminal region of human dopamine %%%transporter%%%
AUTHOR: Lee Ki-Hwan; Kim Mi-Young; Kim Dong-Hwan; Lee Yong-Sung (Reprint)
AUTHOR ADDRESS: Coll MedDept Biochem, Hanyang Univ, 17 Haengdang Dong, Seoul, 133791, South Korea**South Korea
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JOURNAL: Neurochemical Research 29 (7): p1405-1409 July 2004 2004
MEDIUM: print
ISSN: 0364-3190 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The dopamine %%%transporter%%% (DAT) regulates the extent and duration of dopamine %%%receptor%%% activation through sodium-dependant reuptake of dopamine into presynaptic neurons, resulting in termination of dopaminergic neurotransmission. Using the yeast two-hybrid system, we have identified novel interactions between DAT, the SNARE protein syntaxin 1A, and the %%%receptor%%% for activated C kinases (RACK1). This association involves the intracellular N-terminal domain of human DAT (hDAT). Our data suggest that hDAT may exist as dimers or oligomers and that its protein-protein interactions with syntaxin 1A and RACK1 form functional regulatory complexes that may mediate DAT trafficking through modulation of hDAT phosphorylation by PKC.

8/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014808212 BIOSIS NO.: 200400178969
Increased particulate partitioning of PKCepsilon reverses susceptibility of phospholamban knockout hearts to ischemic injury.
AUTHOR: Gregory Kimberly N; Hahn Harvey; Haghighi Kobra; Marreez Yehia; Odley Amy; Dorn Gerald W; Kranias Evangelia G (Reprint)
AUTHOR ADDRESS: Department of Pharmacology and Cell Biophysics, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH, 45267 0575, USA**USA
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JOURNAL: Journal of Molecular and Cellular Cardiology 36 (2): p313-318 February 2004 2004
MEDIUM: print
ISSN: 0022-2828 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytosolic Ca2+ overload is a critical mediator of myocardial damage following cardiac ischemia-reperfusion. It has therefore been proposed that normalization of sarcoplasmic reticulum Ca2+ cycling through inhibition or ablation of the Ca2+ ATP-ase inhibitor phospholamban (PLN), which shows promise as a treatment for heart failure, could be beneficial in ischemic heart disease. However, a recent study has shown that globally ischemic PLN-deficient hearts exhibit increased ischemic injury, with impaired contractile, ATP, and phosphocreatine recoveries, compared to wild-type hearts. Since protein kinase C (PKC) family members are widely recognized as mediators of both post-ischemic injury and ischemic preconditioning, we assessed PKC levels in PLN-deficient hearts. Compared to genetically normal hearts, PLN-deficient hearts exhibited diminished particulate partitioning of PKCepsilon, a known cardioprotective PKC isoform, without alterations in the levels of membrane-associated PKCdelta nor PKCalpha. To determine if decreased particulate partitioning of cardioprotective PKCepsilon was a cause of increased ischemic injury in PLN-deficient hearts, PLN-deficient

mice were mated with mice expressing a myocardial-specific PKCepsilon translocation activator peptide, pseudo-epsilon %%%receptor%%% for activated kinase C (psiepsilonRACK). In psiepsilonRACK/PLN knockout (KO) hearts, PKCepsilon translocation to membranous cellular structures was augmented and this was associated with a significant acceleration of post-ischemic contraction and relaxation rates, as well as reduction of creatine phosphokinase release, compared to PLN-deficient hearts. Importantly, post-ischemic functional recovery reached pre-ischemic hyperdynamic values in psiepsilonRACK/PLN KO hearts, indicating super-rescue by the combination of PLN ablation and psiepsilonRACK expression. These findings suggest that diminished PKCepsilon particulate partitioning in PLN-deficient hearts is associated with attenuated contractile recovery upon ischemia-reperfusion and that increased translocation of PKCepsilon to membranous cellular structures confers full cardioprotection.

8/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014438112 BIOSIS NO.: 200300396542
Human malaria parasites display a %%%receptor%%% for activated C kinase ortholog.
AUTHOR: Madeira Luciana; DeMarco Ricardo; Gazarini Marcos L; Verjovski-Almeida Sergio; Garcia Celia R S (Reprint)
AUTHOR ADDRESS: Departamento de Fisiologia, Instituto de Biociencias, Universidade de Sao Paulo, Rua do Matao, travessa 14, n321, 05508-900, Sao Paulo, SP, Brazil**Brazil
AUTHOR E-MAIL ADDRESS: cgarcia@usp.br
JOURNAL: Biochemical and Biophysical Research Communications 306 (4): p 995-1001 July 11, 2003 2003
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Receptors for activated C kinases (RACKs) are scaffold proteins that anchor diverse signaling proteins and are involved in modulating cell cycle. We report the cloning and cellular localization of a %%%RACK%%% ortholog (PfRACK) in the human malaria parasite Plasmodium falciparum. The full-length transcript obtained by 3' and 5' RACE has 1.4 kbp with a predicted ORF of 972 bp, coding for a protein with 323 residues of 35.8 kDa molecular weight and pI 6.38. PfRACK has 59% and 60% identity at the amino acid level to Chlamydomonas reinhardtii and Danio rerio RACKs, respectively, presenting seven WD40 motifs and retaining the conserved domains in repeats III (DVFSVSF) and VI (STINSLCF) that are important for PKC binding. Semi-quantitative RT-PCR revealed that PfRACK is constitutively expressed in the intraerythrocytic stages of P. falciparum. Using confocal microscopy, PfRACK was immunolocalized in all parasite stages, being conspicuously spread throughout the schizont. The high similarity of PfRACK to those previously described in other organisms, as well as its constitutive expression in Plasmodium asexual stages, suggests that it might play a key role in the regulatory processes of malaria parasite life cycle.

8/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014120530 BIOSIS NO.: 200300079249
The cyclin-dependent kinase inhibitor p27KIP1 binds to RACK1 and regulates protein kinase Cbeta2 in cardiomyocytes.
AUTHOR: Hauck Ludger (Reprint); Dietz Rainer (Reprint); von Harsdorf Ruediger (Reprint)
AUTHOR ADDRESS: Medicine Clin mit Schwerpunkt Kardiologie, Universitaetsklinikum Charite, Berlin, Germany**Germany
JOURNAL: Circulation 106 (19 Supplement): pII-33 November 5, 2002 2002
MEDIUM: print

CONFERENCE/MEETING: Abstracts from Scientific Sessions Chicago, IL, USA November 17-20, 2002; 20021117
SPONSOR: American Heart Association
ISSN: 0009-7322 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

8/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013834550 BIOSIS NO.: 200200428061
Impaired protein kinase C activation/translocation in Epstein-Barr virus-infected monocytes
AUTHOR: Tardif Melanie; Savard Martin; Flamand Louis; Gosselin Jean (Reprint)
AUTHOR ADDRESS: Laboratory of Viral Immunology, Centre de Recherche en Rhumatologie et Immunologie, CHUL Research Center (CHUQ), 2705 Boul. Laurier, Rm. T 1-49, Sainte-Foy, PQ, G1V 4G2, Canada**Canada
JOURNAL: Journal of Biological Chemistry 277 (27): p24148-24154 July 5, 2002 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Infection of human monocytes by Epstein-Barr virus (EBV) has been linked to a decrease in the production of proinflammatory mediators as well as an impairment of phagocytosis. Considering the key role of protein kinases C (PKCs) in many biological functions of monocytes, including phagocytosis, we investigated the effects of EBV on the PKC activity in infected monocytes. Our results indicate that infection of monocytes by EBV impairs both phorbol 12-myristate 13-acetate (PMA)-induced translocation of PKC isozymes alpha and beta from cytosol to membrane as well as the PKC enzymatic activity. Similarly, the subcellular distribution of the %%%receptor%%% for activated C kinase (%%%RACK%%%), an anchoring protein essential to PKC translocation, was also found to be reduced in EBV-infected monocytes. Transfection of 293T cells with an expression vector coding for the immediate-early protein ZEBRA of EBV resulted in impaired PMA-induced translocation and activity of PKC. Using co-immunoprecipitation assays, the ZEBRA protein was found to physically interact with the RACK1 protein. Thus interaction of ZEBRA with %%%RACK%%% likely results in the inhibition of PKC activity, which in turn affects functions of monocytes, such as phagocytosis.

8/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013485553 BIOSIS NO.: 200200079064
Enhanced PKCbetaII translocation and PKCbetaII-RACK1 interactions in PKCepsilon-induced heart failure: A role for RACK1
AUTHOR: Pass Jason M; Gao Jiuming; Jones W Keith; Wead William B; Wu Xin; Zhang Jun; Baines Christopher P; Bolli Roberto; Zheng Yu-Ting; Joshua Irving G; Ping Peipei (Reprint)
AUTHOR ADDRESS: Cardiology Research, 570 S. Preston St., Baxter Bldg., Suite 122, Louisville, KY, 40202-1783, USA**USA
JOURNAL: American Journal of Physiology 281 (6 Part 2): pH2500-H2510 December, 2001 2001
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent investigations have established a role for the betaII-isoform of protein kinase C (PKCbetaII) in the induction of

cardiac hypertrophy and failure. Although receptors for activated C kinase (RACKs) have been shown to direct PKC signal transduction, the mechanism through which RACK1, a selective PKCbetaII %%%RACK%%%, participates in PKCbetaII-mediated cardiac hypertrophy and failure remains undefined. We have previously reported that PKCepsilon activation modulates the expression of RACKs, and that altered epsilon-isoform of PKC (PKCepsilon)-%%%RACK%%% interactions may facilitate the genesis of cardiac phenotypes in mice. Here, we present evidence that high levels of PKCepsilon activity are commensurate with impaired left ventricular function (dP/dt = 6,074 +- 248 mmHg/s in control vs. 3,784 +- 269 mmHg/s in transgenic) and significant myocardial hypertrophy. More importantly, we demonstrate that high levels of PKCepsilon activation induce a significant colocalization of PKCbetaII with RACK1 (154 +- 7% of control) and a marked redistribution of PKCbetaII to the particulate fraction (17 +- 2% of total PKCbetaII in control mice vs. 49 +- 5% of total PKCbetaII in hypertrophied mice), without compensatory changes of the other eight PKC isoforms present in the mouse heart. This enhanced PKCbetaII activation is coupled with increased RACK1 expression and PKCbetaII-RACK1 interactions, demonstrating PKCepsilon-induced PKCbetaII signaling via a RACK1-dependent mechanism. Taken together with our previous findings regarding enhanced RACK1 expression and PKCepsilon-RACK1 interactions in the setting of cardiac hypertrophy and failure, these results suggest that RACK1 serves as a nexus for at least two isoforms of PKC, the epsilon-isoform and the betaII-isoform, thus coordinating PKC-mediated hypertrophic signaling.

8/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013364804 BIOSIS NO.: 200100536643
Cardiac hypertrophy and failure: Lessons learned from genetically engineered mice
AUTHOR: Takeishi Y; Walsh R A (Reprint)
AUTHOR ADDRESS: Department of Medicine, Case Western Reserve University and University Hospitals of Cleveland, 11100 Euclid Avenue, LKS 3563, Cleveland, OH, 44106-5029, USA**USA
JOURNAL: Acta Physiologica Scandinavica 173 (1): p103-111 September, 2001
2001
MEDIUM: print
ISSN: 0001-6772
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Congestive heart failure is a major and growing public health problem. Because of improved survival of myocardial infarction patients produced by thrombolytic therapy or per-cutaneous revascularization it represents the only form of cardiovascular disease with significantly increased incidence and prevalence. Clinicians view this clinical syndrome as the final common pathway of diverse pathologies such as myocardial infarction and haemodynamic overload. Insights into mechanisms for heart failure historically derived from physiological and biochemical studies which identified compensatory adaptations for the haemodynamic burden associated with the pathological condition including utilization of the Frank Starling mechanism, augmentation of muscle mass, and neurohormonal activation to increase contractility. Therapy has largely been phenomenological and designed to prevent or limit the deleterious effects of these compensatory processes. More recently insights from molecular and cell biology have contributed to a more mechanistic understanding of potential causes of cardiac hypertrophy and failure. Many different analytical approaches have been employed for this purpose. These include the use of conventional animal models which permit serial observation of the onset and progression of heart failure and a sequential analysis of underlying biochemical and molecular events. Neonatal murine cardiomyocytes have been a powerful tool to examine in vitro subcellular mechanisms devoid of the confounding functional effects of multicellular preparations and heterogeneity of cell type. Finally, significant progress has been made by utilizing tissue from human cardiomyopathic hearts explanted at the time of orthotopic

transplantation. Each of these methods has significant advantages and disadvantages. Arguably the greatest advance in our understanding of cardiac hypertrophy and failure over the past decade has been the exploitation of genetically engineered mice as biological reagents to study in vivo the effects of alterations in the murine genome. The power of this approach, in principle, derives from the ability to precisely overexpress or ablate a gene of interest and examine the phenotypic consequences in a cardiac specific post-natal manner. In contrast to conventional animal models of human disease which employ some form of environmental stress, genetic engineering involves a signal known molecular perturbation which produces the phenotype.

8/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013073203 BIOSIS NO.: 200100245042
Induction and subcellular localization of protein kinase C isozymes following renal ischemia
AUTHOR: Padanilam Babu (Reprint)
AUTHOR ADDRESS: Physiology and Biophysics, University of Nebraska Medical Center, Omaha, NE, 68198, USA**USA
JOURNAL: FASEB Journal 15 (4): pA86 March 7, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001; 20010331
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. We have previously reported that the expression of the %%%receptor%%% for activated C kinase (%%%RACK%%% 1) is induced post ischemia/reperfusion injury to the kidney and activation of PKC protects renal cells from hypoxic injury. This study was done to determine if induced expression of RACK1 is accompanied by changes in the level of expression and subcellular distribution of PKC isozymes. Methods. Ischemia/reperfusion injury resulting in acute renal failure was induced by 60 minutes of bilateral renal artery clamping in rats. The expression levels and translocation of various PKC isozymes between soluble and particulate fractions in whole kidney homogenates were demonstrated by immunoblot analysis. The expression pattern of the various PKC isozymes in the kidney post injury was performed by immunohistochemistry. Results. PKC-alpha, beta II and zeta are induced and translocated from the soluble fraction to the particulate fraction post injury. Immunolocalization shows PKC-alpha, beta II and zeta expression to be induced in the proximal tubule epithelial cell (PTEC) at 0-30 min post ischemia/reperfusion injury (IRI). At 1 day post injury, the alpha isozyme is translocated to the plasma membrane of the undamaged PTEC while it is translocated to the nucleus in damaged PTEC. PKC-beta II expression is along the basal and lateral side of the undamaged PTEC while it is along the plasma membrane of sloughed cells in the damaged PTEC. PKC-zeta expression at 1 day is along the apical side of the damaged PTEC. At 7 days post injury, the expressions of the alpha and zeta isozymes are localized to the plasma membrane of the regenerating PTEC and the expression of PKC beta II isozyme to certain interstitial cells. Conclusion: The induced expression, translocation and the intracellular spatial distributions of the PKC isozymes suggest that they may mediate multiple processes during IRI.

8/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012930340 BIOSIS NO.: 200100102179
A %%%receptor%%% for activated C kinase is upregulated by angiotensin II and colocalizes with protein kinase C beta in adult cardiac myocytes
AUTHOR: Rieger Brent S (Reprint); Reed E Beth (Reprint); Geenen David L

(Reprint)
AUTHOR ADDRESS: Univ of Illinois at Chicago, Chicago, IL, USA**USA
JOURNAL: Circulation 102 (18 Supplement): pII.70 October 31, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: Abstracts from American Heart Association Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000; 20001112
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

8/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012928830 BIOSIS NO.: 200100100669
RACK1 is upregulated in angiogenesis and human cancers
AUTHOR: Berns H (Reprint); Humar R (Reprint); Hengerer B; Kiefer F (Reprint); Battegay E J (Reprint)
AUTHOR ADDRESS: Department of Research, Novartis, Basel, Switzerland** Switzerland
JOURNAL: Journal of Submicroscopic Cytology and Pathology 32 (3): p431 July, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: XIth International Vascular Biology Meeting Geneva, Switzerland September 05-09, 2000; 20000905
ISSN: 1122-9497
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

8/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012863702 BIOSIS NO.: 200100035541
Dichotomous cardiac phenotypes are congruous with differential interactions between protein kinase C epsilon and its %%%receptor%%% proteins
AUTHOR: Pass Jason M (Reprint); Zheng Yu-Ting (Reprint); Zhang Jun (Reprint); Li Richard C X (Reprint); Bolli Roberto (Reprint); Ping Peipei (Reprint)
AUTHOR ADDRESS: Univ of Louisville, Louisville, KY, USA**USA
JOURNAL: Circulation 102 (18 Supplement): pII.160 October 31, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: Abstracts from American Heart Association Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000; 20001112
SPONSOR: American Heart Association
ISSN: 0009-7322
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RECORD TYPE: Citation
LANGUAGE: English

8/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012205121 BIOSIS NO.: 199900464781
Association of RACK1 and PKCbeta with the common beta-chain of the IL-5/IL-3/GM-CSF %%%receptor%%%
AUTHOR: Geijsen Niels; Spaargaren Marcel; Raaijmakers Jan AM; Lammers Jan-Willem J; Koenderman Leo; Coffer Paul J (Reprint)
AUTHOR ADDRESS: Department of Pulmonary Diseases, University Hospital Utrecht, Heidelberglaan 100, 3508 GA, Utrecht, Netherlands**Netherlands
JOURNAL: Oncogene 18 (36): p5126-5130 Sept. 9, 1999 1999
MEDIUM: print
ISSN: 0950-9232
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-3 (IL-3) and interleukin-5 (IL-5 belong to a family of cytokines that regulate proliferation, differentiation and function of haematopoietic cells. Their %%%receptor%%% consists of a ligand specific alpha-chain and a signal transducing beta-chain (betac). While, the role of phosphotyrosine residues in the betac as mediators of downstream signalling cascades has been established, little is known about non-phosphotyrosine mediated events. To identify proteins interacting with betac, we screened a yeast two-hybrid library with the intracellular domain of betac. We found that RACK1, a molecule associating with activated PKC, PLCgamma and Src kinases, associated with the membrane proximal region of betac in both yeast two-hybrid, immunoprecipitation and GST-pull-down assays. The association of RACK1 was constitutive, demonstrating no alteration upon cellular stimulation. Furthermore, upon stimulation of cells with IL-5 or PMA, a complex of betacand PKCbeta was found. Together, these findings suggest a novel role for RACK1 as a possible adapter molecule associating with the intracellular domain of cytokine receptors.

8/7/16 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14494443 PMID: 12437589
The anti-inflammatory activity of estrogen in glial cells is regulated by the PKC-anchoring protein %%%RACK%%%-1.

Viviani Barbara; Corsini Emanuela; Binaglia Marco; Lucchi Laura; Galli Corrado L; Marinovich Marina
Centre of Excellence on Neurodegenerative Diseases and Laboratory of Toxicology, Department of Pharmacological Sciences, University of Milan, Milan, Italy. Barbara.Viviani@unimi.it

Journal of neurochemistry (England) Dec 2002, 83 (5) p1180-7, ISSN 0022-3042 Journal Code: 2985190R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

It has recently been suggested that estrogen inhibits glial activation and the release of neurotoxic mediators. The mechanisms involved in this anti-inflammatory effect are unclear. We found that an nM concentration of 17-beta estradiol inhibits protein kinaseC-betaII translocation induced by lipopolysaccharide in primary astrocytes. Estradiol treatment did not change the total content of kinaseC-betaII or of lipopolysaccharide %%%receptor%%% , but dose-dependently reduced the levels of receptors for activated C kinases-1 (%%%RACK%%% -1), the anchoring protein involved in protein kinase C (PKC) shuttling. This decrease could thus account for the defective protein kinaseC-betaII activation. Pre-treatment with 1 nmbeta-estradiol, which reduced by approximately 35% the expression of %%%RACK%%%-1, prevented the lipopolysaccharide-induced expression of tumour necrosis factor-alpha mRNA and of the inducible form of nitric oxide (NO) synthase. As a consequence, the production of tumour necrosis factor-alpha and NO were decreased. An antisense oligonucleotide for %%%RACK%%%-1 also reduced tumour necrosis factor-alpha and nitric oxide production on lipopolysaccharide stimulation. These results demonstrate that estrogen reduction of the %%%RACK%%%-1 expression, leading to a defective protein kinase-C activation counteracts the inflammatory response in astrocytes.

Record Date Created: 20021119
Record Date Completed: 20030116

8/7/17 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13993205 PMID: 11744093
Dehydroepiandrosterone and the relationship with aging and memory: a

possible link with protein kinase C functional machinery.
Racchi M; Govoni S; Solerte S B; Galli C L; Corsini E
Department of Experimental and Applied Pharmacology, University of Pavia, Viale Taramelli 14, 27100, Pavia, Italy. racchi@unipv.it
Brain research. Brain research reviews (Netherlands) Nov 2001, 37 (1-3) p287-93, ISSN 0165-0173 Journal Code: 8908638
Publishing Model Print
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

A progressive decline of cognitive and memory functions, compared to the average young-life performance, characterizes brain aging. The changes in performance may depend upon altered activity of neurotransmitters acting on attention and memory trace formation (acetylcholine, catecholamines, glutamate, for example) or the failure of the transduction mechanisms linked to %%%receptor%%% activation. One of the fundamental cellular changes associated with brain aging is the alteration of mechanisms involving the activity of the calcium-phospholipid-dependent protein kinase C (PKC). A crucial event for the activation of protein kinase C is its translocation from the cytosol to different intracellular sites and recent studies have demonstrated the key role played by several anchoring proteins in this mechanism. The defective activation of PKC-dependent pathways during aging is due to a defective mechanism of translocation of the kinase because of reduced levels of the major anchoring protein %%%RACK%%%-1 (%%%receptor%%% for activated C kinase). Pharmacological strategies aimed at the correction of age-associated memory deficits have been mostly focused on neurotransmitters using direct or indirect agonists. More recently, attention has been paid to the memory enhancing properties of some steroid hormones, namely 'neurosteroids'. Among these the activities of dehydroepiandrosterone (DHEA), pregnenolone (PREG) and their sulfates, have been extensively studied. These neuroactive steroids can regulate neuronal function through their concurrent influence on transmitter-gated ion channels and gene expression. We addressed the possibility that DHEA, among other neurosteroids, could modulate directly the age-associated impairment of PKC signal transduction and provide experimental evidence that DHEA can revert the alteration of %%%RACK%%%-1 anchoring protein expression. (50 Refs.)

Record Date Created: 20011217
Record Date Completed: 20020211

8/7/18 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11768477 PMID: 8999804
Translocation inhibitors define specificity of protein kinase C isoenzymes in pancreatic beta-cells.
Yedovitzky M; Mochly-Rosen D; Johnson J A; Gray M O; Ron D; Abramovitch E ; Cerasi E; Nesher R
Department of Endocrinology and Metabolism, Hebrew University-Hadassah Medical Center, 91120 Jerusalem, Israel.
Journal of biological chemistry (UNITED STATES) Jan 17 1997, 272 (3) p1417-20, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: HL43380; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The protein kinase C (PKC) family consists of 11 isoenzymes. Following activation, each isoenzyme translocates and binds to a specific %%%receptor%%% for activated C kinase (%%%RACK%%%) (Mochly-Rosen, D. (1995) Science 268, 247-251) that provides an anchoring site in close proximity to the isoenzyme's specific substrate. Pancreatic islet cells contain at least six PKC isoenzymes (Knutson, K. L., and Hoenig, M. (1994) Endocrinology 135, 881-886). Although PKC activation enhances insulin release, the specific function of each isoenzyme is unknown. Here we show that following stimulation with glucose, alphaPKC and epsilonPKC translocate to the cell's periphery, while deltaPKC and zetaPKC translocate to perinuclear sites.

betaC2-4, a peptide derived from the RACK1-binding site in the C2 domain of betaPKC, inhibits translocation of alphaPKC and reduces insulin response to glucose. Likewise, epsilonV1-2, an epsilonPKC-derived peptide containing the site for its specific %%%RACK%%%, inhibits translocation of epsilonPKC and reduces insulin response to glucose. Inhibition of islet-glucose metabolism with mannoheptulose blocks translocation of both alphaPKC and epsilonPKC and diminishes insulin response to glucose while calcium-free buffer inhibits translocation of alphaPKC but not epsilonPKC and lowers insulin response by 50%. These findings illustrate the unique ability of specific translocation inhibitors to elucidate the isoenzyme-specific functions of PKC in complex signal transduction pathways.
Record Date Created: 19970213
Record Date Completed: 19970213

? t s12/7/1-32

12/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015621854 BIOSIS NO.: 200510316354
Activated E-protein kinase C accelerates the transition from compensatory left ventricular hypertrophy to heart failure in hypertensive rats
AUTHOR: Inagaki Koichi (Reprint); Begley Rebecca; %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94305 USA**USA
JOURNAL: Circulation 110 (17, Suppl. S): p598 OCT 26 2004 2004
CONFERENCE/MEETING: 77th Scientific Meeting of the American-Heart-Association New Orleans, LA, USA November 07 -10, 2004; 20041107
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: We have previously demonstrated that epsilon protein kinase C (epsilon PKC) levels are increased in compensatory hypertrophied left ventricle (LV) in Dahl salt-sensitive rats with systemic hypertension, and the activation of epsilon PKC induces the physiological LV hypertrophy without impaired cardiac function in transgenic mice expressing the epsilon PKC selective activator peptice (Psi epsilon %%%RACK%%%). Hypothesis: Here, we hypothesized that epsilon PKC signaling is necessary to maintain compensatory hypertrophy and thus the treatment with IVERACK should prevents the progression of heart failure. Methods: Dahl salt-sensitive rats were fed with 8% salt diet from 6 weeks old to induce systemic hypertension. Dahl salt-sensitive rats were treated continuously with Psi epsilon %%%RACK%%% (n=15) or with control carrier peptice Tat (n=12) from 15 to 17 weeks old using subcutaneously implanted osmotic pump. Cardiac function was determined by echocardiography. Results: The treatment with Psi epsilon %%%RACK%%% before the transition to heart failure shortened the survival rate (Psi epsilon %%%RACK%%% 118.9 +/- 2.8 vs. control 138.5 +/- 10.3 days old, P<0.05). In addition, the treatment with Psi epsilon %%%RACK%%% resulted in reduced fractional shortening (Psi epsilon %%%RACK%%% 35.9 +/- 3.3 vs. control 46.5 +/- 2.6 %, P<0.05), increased LV end diastolic dimension (Psi epsilon %%%RACK%%% 8.3 +/- 0.4 vs. control 7.5 +/- 0.2 mm, P<0.05), increased systolic wall stress (Psi epsilon %%%RACK%%% 139.0 +/- 25.4 vs. control 85.3 +/- 7.2 g/cm(2), P<0.05), and increased LV weight (Psi epsilon %%%RACK%%% 1.38 +/- 0.05 vs. control 1.22 +/- 0.04 g, P<0.05) and lung weight (Psi epsilon %%%RACK%%% 3.28 +/- 0.98 vs. control 1.73 +/- 0.1 g, P<0.05) as compared with the treatment with the control peptice at 17 weeks old. There were no significant differences between the two groups in systolic blood pressure (Psi epsilon %%%RACK%%% 255.2 +/- 7.9 vs. control 247.9 +/- 4.7 mmHg) and in body weight (Psi epsilon %%%RACK%%% 345.4 +/- 16.4 vs. control 354.2 +/- 13.0 g). Conclusion: Continuous activation of epsilon PKC in hypertrophied LV myocardium of hypertensive rats induces further myocardial hypertrophy, but accelerates the transition to heart failure in contrast to our initial hypothesis.

12/7/2 (Item 2 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

0015619212 BIOSIS NO.: 200510313712
An E-PKC activator reduces ventricular fibrillation, and a Delta-PKC inhibitor prevents stunning in a porcine model of acute myocardial infarction
AUTHOR: Inagaki Koichi (Reprint); Ikeno Fumiaki; %%%Mochly-Rosen Dana%%%
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94305 USA**USA
JOURNAL: Circulation 110 (17, Suppl. S): p28 OCT 26 2004 2004
CONFERENCE/MEETING: 77th Scientific Meeting of the American-Heart-Association New Orleans, LA, USA November 07 -10, 2004; 20041107
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: Previous studies have demonstrated that an epsilon protein kinase C (PKC)-selective activator peptide (psi epsilon %%%RACK%%%) mimics ischemic preconditioning and a delta PKC-selective inhibitor peptide (delta V1-1) prevents reperfusion injury in an isolated perfused rat heart model or in a porcine model. Hypothesis: Here, we hypothesized that the combined treatment with these PKC regulators enhances cardioprotection in an in vivo porcine heart model of acute myocardial infarction. Methods: The left anterior descending artery (LAD) was occluded for 30 minutes using a balloon catheter. psi epsilon %%%RACK%%% was injected to the ischemic area through the lumen of the balloon catheter during the first 10 minutes of ischemia. delta V1-1 was injected to ischemic area during the last 1 minute of ischemia (n=12-16 for each group). Results: The treatment with either psi epsilon %%%RACK%%% or delta V1-1 reduced infarct size by similar to 70% in the similar level as compared with control. psi epsilon %%%RACK%%%, but not delta V1-1, reduced the incidence of ventricular fibrillation (VF) during ischemia/reperfusion. In contrast, delta V1-1, but not psi epsilon %%%RACK%%%, improved cardiac function immediately after reperfusion. Furthermore, when psi epsilon %%%RACK%%% was injected for the first 10 minutes of ischemia followed by delta V1-1 injection for the last 1 minute of ischemia, this combined treatment with delta V1-1 and psi epsilon %%%RACK%%% further reduced infarct size (control, 32.3 +/- 2.4%, psi epsilon %%%RACK%%%; 13.9 +/- 1.4%, delta V1-1; 9.3 +/- 1.1%, combined treatment; 4.5 +/- 1.4%; P<0.05 as compared with control, psi epsilon %%%RACK%%% or delta V1-1, alone), The combined treatment also reduced the incidence of VF during ischemia/reperfusion (control; 88%, psi epsilon %%%RACK%%%; 25%, delta V1-1. 64%, combined treatment; 38%; P<0.05 as compared with control or delta V1-1 alone) and improved ejection fraction immediately after reperfusion (control; 38.3 +/- 2.9%, psi epsilon %%%RACK%%%; 42.5 +/- 3.7%, delta V1-1; 48.4 +/- 3.7%, combined treatment; 53.2 +/- 1.7%; P<0.05 as compared with control or psi epsilon %%%RACK%%% alone). Conclusion: An epsilon PKC activator reduced the incidence of VF, a delta PKC inhibitor prevented cardiac stunning, and the combined treatment with these PKC regulators conferred additive beneficial effects in cardiac damage, arrhythmia and cardiac function. Thus, the combined treatment with an epsilon PKC activator and a delta PKC inhibitor may be useful for the treatment of acute myocardial infarction.

12/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015616842 BIOSIS NO.: 200510311342
PKC-epsilon-dependent survival signals in diabetic hearts
AUTHOR: Malhotra Ashwani (Reprint); Begley Rebecca; Kang Barinder P S; Rana Irmindra; Liu Jing; Yang Guiping; %%%Mochly-Rosen Daria%%%; Meggs Leonard G
AUTHOR ADDRESS: Univ Med and Dent New Jersey, New Jersey Med Sch, Dept Med, Div Nephrol and Hypertens, MSB I-524,185 S Orange Ave, Newark, NJ 07103 USA**USA
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JOURNAL: American Journal of Physiology - Heart and Circulatory Physiology 289 (4): pH1343-H1350 OCT 2005 2005
ISSN: 0363-6135
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Diabetes mellitus is complicated by the development of a primary cardiomyopathy, which contributes to the excess morbidity and mortality of this disorder. The protein kinase C (PKC) family of isozymes plays a key role in the cardiac phenotype expressed during postnatal development and in response to pathological stimuli. Hyperglycemia is an activating signal for cardiac PKC isozymes that modulate a myriad of cell events including cell death and survival. The epsilon-isozyme of the PKC family transmits a powerful survival signal in cardiac muscle cells. Accordingly, to test the hypothesis that endogenous activation of cardiac PKC-epsilon will protect against hyperglycemic cell injury and left ventricular dysfunction, diabetes mellitus was induced using streptozotocin in genetically engineered mice with cardiac-specific expression of the PKC-epsilon translocation activator [psi epsilon-receptors for activated C kinase (psi epsilon-%%%RACK%%%)]. The results demonstrate a striking PKC-epsilon cardioprotective phenotype in diabetic psi epsilon-%%%RACK%%% (epsilon-agonist) mice that is characterized by inhibition of the hyperglycemia apoptosis signal, attenuation of hyperglycemia-mediated oxidative stress, and preservation of parameters of left ventricular pump function. Hearts of diabetic epsilon-agonist mice exhibited selective trafficking of PKC-epsilon to membrane and mitochondrial compartments, phosphorylation/inactivation of the mitochondrial Bad protein, and inhibition of cytochrome c release. We conclude that activation of endogenous PKC-epsilon in hearts of diabetic epsilon-agonist mice promotes the survival phenotype, attenuates markers of oxidative stress, and inhibits the negative inotropic properties of chronic hyperglycemia.

12/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015544562 BIOSIS NO.: 200510239062
delta PKC-mediated activation of epsilon PKC in ethanol-induced cardiac protection from ischemia
AUTHOR: Inagaki K; %%%Mochly-Rosen D%%% (Reprint
AUTHOR ADDRESS: Stanford Univ, Sch Med, Dept Mol Pharmacol, CCSR, Room 3145A,269 Campus Dr, Stanford, CA 94305 USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Journal of Molecular and Cellular Cardiology 39 (2): p203-211 AUG 2005 2005
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous studies have demonstrated that acute ethanol exposure induces activation of 6 protein kinase C (delta PKC) and epsilon PKC, and mimics ischemic preconditioning via epsilon PKC activation. However, the role of delta PKC isozyme in ischemia and reperfusion is still controversial. Here, we investigated the role of delta PKC in ethanol-induced cardioprotection using a selective delta PKC activator (psi delta %%%RACK%%%), or inhibitor (delta V1-1), and a selective epsilon PKC inhibitor (epsilon V1-2) in isolated mouse hearts. Mice were injected intraperitoneally or by gavage with ethanol, regulators of 6 and epsilon PKC or an adenosine A, receptor blocker (DPCPX). Isolated perfused mouse hearts were subjected to a 30-min global ischemia and a 120-min reperfusion, ex vivo. Injection of 0.5 g/kg ethanol 1 h, but not 10 min, before ischemia reduced infarct size and CPK release. Pretreatment with epsilon V1-2 abolished this ethanol-induced cardioprotection. Pretreatment with delta V1-1 induced cardioprotection when injected with ethanol (0.5 g/kg) 10 min before ischemia, but delta V1-1 partly inhibited ethanol-induced cardioprotection when injected with ethanol 1-h before the onset of ischemia. psi delta %%%RACK%%% injection

1 h, but not 10 min, before ischemia induced cardioprotection and translocation of epsilon PKC from the cytosol to the particulate fraction. Pretreatment with DPCPX or epsilon V1-2 inhibited psi delta %%%RACK%%%-induced cardioprotection and translocation of epsilon PKC. Therefore, activation of epsilon PKC-induced by ethanol or by the delta PKC activator is cardioprotective, provided that sufficient time passes to allow delta PKC-induced activation of epsilon PKC, an A(1) adenosine receptor-dependent process. (c) 2005 Published by Elsevier Ltd.

12/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015518955 BIOSIS NO.: 200510213455
A critical role of mitochondrial aldehyde dehydrogenase in ethanol-induced ePKC-mediated cardioprotection against ischemia/reperfusion damage
AUTHOR: Chen C-H (Reprint); Inagaki K; %%%Mochly-Rosen D%%%
AUTHOR ADDRESS: Stanford Univ, Dept Mol Pharmacol, Stanford, CA 94305 USA** USA
JOURNAL: Alcoholism Clinical and Experimental Research 28 (5, Suppl. S): p 54A MAY 2004 2004
CONFERENCE/MEETING: 27th Annual Meeting of the Research-Society-on-Alcoholism Vancouver, CANADA June 26 -30, 2004; 20040626
SPONSOR: Res Soc Alcoholism
ISSN: 0145-6008
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015491583 BIOSIS NO.: 200510186083
Mechanism of interaction between Annexin V and delta PKC
AUTHOR: Kheifets Viktoria (Reprint); Bright Rachel; Wong Melissa; Kihara Yasuki; %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94205 USA**USA
JOURNAL: FASEB Journal 18 (8, Suppl. S): pC213 MAY 14 2004 2004
CONFERENCE/MEETING: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology Boston, MA, USA June 12 -16, 2004; 20040612
SPONSOR: Amer Soc BioChem & Mol Biol
Int Union Biochem & Mol Biol
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Annexins form a family of calcium-dependent membrane-binding proteins. At present, 13 members of the family have been identified. The physiological role of these highly abundant cytosolic proteins is currently not known. However, a number of links exist between the annexins and the protein kinase C family that consists of at least I I members, exhibiting isozyme-specific localization, translocation, and functional profiles. Annexins associate with PKC isozymes; some are substrates of specific PKC isozymes, whereas others are inhibitors. Activation of PKC and its subsequent translocation to the cell membrane results in protection of the heart from myocardial ischemia. JTV519, a benzothiazepine derivative, protects hearts from ischemic injury and from Ca2+ overload-induced myocardial injury. JTV519 binds tightly to annexin V and is thought to confer its protective effect through this interaction. In addition, JTV519 treatment of cardiac myocytes causes translocation of delta PKC to the cell membrane. Furthermore, Annexin V contains a sequence that closely resembles a sequence found on delta PKC in a location that has previously been found to be involved in inhibitory intramolecular interaction, the pseudo-%%%RACK%%% site. In this study,we

investigate the exact mechanism of interaction between annexin V and deltaPKC. We show that the interaction occurs through the VI domain of delta PKC in an isozyme-selective manner using both overlay and pulldown assays. We also show that peptides that most closely resemble the annexin V sequence bind to delta PKC. Co-immunoprecipitation studies from neonatal cardiac myocytes show that annexin V and delta PKC interaction is dependent on cell activation state.Together, these studies indicate a mechanism for both the interaction of annexin V and delta PKC as well as the mechanism for the protection of the heart by both a delta PKC activator and JTV519.

12/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015490717 BIOSIS NO.: 200510185217
The role of the V5 domain of epsilon PKC in enzyme function and localization
AUTHOR: Kheifets Viktoria (Reprint); Schechtman Deborah; Craske Madeleine; %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94205 USA**USA
JOURNAL: FASEB Journal 18 (8, Suppl. S): pC24 MAY 14 2004 2004
CONFERENCE/MEETING: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology Boston, MA, USA June 12 -16, 2004; 20040612
SPONSOR: Amer Soc BioChem & Mol Biol
Int Union Biochem & Mol Biol
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein kinase C family consists of at least I I members subdivided into classical, novel, and atypical groups. In the inactive state, the phospholipid-binding site in the C2/V1 domain and the catalytic site in the C3-C4 of PKC isozymes are inaccessible. Upon activation, these sites become exposed, resulting inPKC translocation and substrate phosphorylation. Inhibitory intramolecular interactions, which are broken upon activation, keep the enzyme in the inactive state. The binding of the pseudo-substrate site into the active site of the enzyme is an example of such intramolecular interaction in PKC. We showed that another inhibitory intramolecular interaction occurs between the pseudo-%%%RACK%%% site and the %%%RACK%%%-binding site. We have recently established that mutation of the pseudo-%%%RACK%%% site alters the translocation kinetics and conformation of the enzyme. Here, we tested the hypothesis that for epsilon PKC, the %%%RACK%%%-binding site that interacts with the pseudo-%%%RACK%%% is located in V5 domain. We first showed in an isozyme-specific manner that the VI and V5 domains interact in vitro.Whereas the wild-type epsilon PKC is cytosolic in the inactive state, deletion of the V5 region resulted in altered localization of the enzyme to the membrane in the absence of activators. In fact, deletion of as little as 10 amino acids of the V5 domain results in membrane bound enzyme. The V5 domain deletionmutants were unable to translocate further in response to activation with PMA. However, co-transfection of the V5-delition mutant with the wildtype enzyme was able to restore the V5-delition mutant to the cytosol, where it became responsive to activation by PMA by translocating to the membrane. Together, thesedata suggest the importance of the V5 domain in mediating an inhibitory intramolecular interaction within ePKC that masks the lipid-binding domain. It remains to be deter-mined whether the wild-type enzyme affects the localization ofthe V5 deletion mutant by either direct interaction (dimerization), or by modification (phosphorylation).

12/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015186866 BIOSIS NO.: 200500092779

Cardioprotection by epsilon-protein kinase C activation from ischemia - Continuous delivery and antiarrhythmic effect of an epsilon-protein kinase C-activating peptide
AUTHOR: Inagaki Koichi; Begley Rebecca; Ikeno Fumiaki; %%%Mochly-Rosen%%% %%% Daria%%% (Reprint
AUTHOR ADDRESS: Sch MedDept Mol Pharmacol, Stanford Univ, 269 Campus Dr,3145 CCSR, Stanford, CA, 94305, USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Circulation 111 (1): p44-50 January 4, 2005 2005
MEDIUM: print
ISSN: 0009-7322 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background - We previously showed that a selective activator peptide of epsilon-protein kinase C (PKC), psiepsilonRACK, conferred cardioprotection against ischemia-reperfusion when delivered ex vivo before the ischemic event. Here, we tested whether in vivo continuous systemic delivery of psiepsilonRACK confers sustained cardioprotection against ischemia-reperfusion in isolated mouse hearts and whether psiepsilonRACK treatment reduces infarct size or lethal arrhythmias in porcine hearts in vivo. Methods and Results - After psiepsilonRACK was systemically administered in mice either acutely or continuously, hearts were subjected to ischemia-reperfusion in an isolated perfused model. Whereas psiepsilonRACK-induced cardioprotection lasted 1 hour after a single intraperitoneal injection, continuous treatment with psiepsilonRACK induced a sustained preconditioned state during the 10 days of delivery. There was no desensitization to the therapeutic effect, no downregulation of epsilonPKC, and no adverse effects after sustained psiepsilonRACK delivery. Porcine hearts were subjected to ischemia-reperfusion in vivo, and psiepsilonRACK was administered by intracoronary injection during the first 10 minutes of ischemia. psiepsilonRACK treatment reduced infarct size (34+/-2% versus 14+/-1%, control versus psiepsilonRACK) and resulted in fewer cases of ventricular fibrillation during ischemia-reperfusion (87.5% versus 50%, control versus psiepsilonRACK). Conclusions - The epsilonPKCactivator psiepsilonRACK induced cardioprotection both in vivo and ex vivo, reduced the incidence of lethal arrhythmia during ischemia-reperfusion, and did not cause desensitization or downregulation of epsilonPKC after sustained delivery. Thus, psiepsilonRACK may be useful for patients with ischemic heart disease. In addition, the psiepsilonRACK peptide should be a useful pharmacological agent for animal studies in which systemic and sustained modulation of epsilonPKC in vivo is needed.

12/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014984461 BIOSIS NO.: 200400355250
RACK1 regulates Src-mediated Sam68 and p190RhoGAP signaling
AUTHOR: Miller Laura D; Lee Kelly C; %%%Mochly-Rosen Darla%%%; Cartwright Christine A (Reprint
AUTHOR ADDRESS: Dept MedSch Med, Stanford Univ, M211 Alway Bldg,300 Pasteur Dr, Stanford, CA, 94305, USA**USA
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JOURNAL: Oncogene 23 (33): p5682-5686 July 22, 2004 2004
MEDIUM: print
ISSN: 0950-9232 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: RACK1 is the founding member of a family of receptors for activated C kinase collectively called RACKs. Upon activation of PKC, RACK1 co-localizes with the Src tyrosine kinase at the plasma membrane and functions as a substrate, binding partner and inhibitor of Src (as measured in vitro), and a growth inhibitor in NIH 3T3 cells. To further analyze the function of RACK1 in Src and PKC signaling, we utilized cell-permeable peptides that modulate the interaction of RACK1 and

betaIIPKC, thereby affecting betaIIPKC translocation and function. We found that the association of betaIIPKC and RACK1 is necessary for Src phosphorylation of RACK1. Src activity is required for tyrosine phosphorylation of RACK1, and for RACK1 binding to Src, but not to betaIIPKC. Endogenous Src kinase activity, as measured by phosphorylation of Sam68 (a mitotic-specific Src substrate involved in cell cycle regulation and RNA splicing) or p190RhoGAP (a Src substrate and GTPase-activating protein involved in actin reorganization), increases with disruption of the Src-RACK1 complex, and decreases with enhanced complex formation. RACK1 inhibits Src-mediated p190RhoGAP signaling and actin cytoskeleton rearrangement. Thus, RACK1 functions as an endogenous inhibitor of the Src kinase in diverse signaling pathways that regulate distinct cellular functions. Our results demonstrate the potential for using peptide modulators of Src activity as a tool for uncovering the function of Src in cells.

12/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014948590 BIOSIS NO.: 200400119347
A critical intramolecular interaction for protein kinase Cepsilon translocation
AUTHOR: Schechtman Deborah; Craske Madeleine L; Kheifets Viktoria; Meyer Tobias; Schechtman Jack; %%%Mochly-Rosen Daria%%% (Reprint
AUTHOR ADDRESS: Sch MedDept Mol PharmacolCCSR 3145, Stanford Univ, 269 Campus Dr, Stanford, CA, 94305, USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Journal of Biological Chemistry 279 (16): p15831-15840 April 16, 2004 2004
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Disruption of intramolecular interactions, translocation from one intracellular compartment to another, and binding to isozyme-specific anchoring proteins termed RACKs, accompany protein kinase C (PKC) activation. We hypothesized that in inactive epsilonPKC, the %%%RACK%%% -binding site is engaged in an intramolecular interaction with a sequence resembling its %%%RACK%%%, termed psiepsilonRACK. An amino acid difference between the psiepsilonRACK sequence in epsilonPKC and its homologous sequence in epsilonACK constitutes a change from a polar non-charged amino acid (asparagine) in epsilonRACK to a polar charged amino acid (aspartate) in epsilonPKC. Here we show that mutating the aspartate to asparagine in epsilonPKC increased intramolecular interaction as indicated by increased resistance to proteolysis, and slower hormone- or PMA-induced translocation in cells. Substituting aspartate for a non-polar amino acid (alanine) resulted in binding to epsilonRACK without activators, in vitro, and increased translocation rate upon activation in cells. Mathematical modeling suggests that translocation is at least a two-step process. Together our data suggest that intramolecular interaction between the psiRACK site and %%%RACK%%% -binding site within epsilonPKC is critical and rate limiting in the process of PKC translocation.

12/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014899945 BIOSIS NO.: 200400270702
State-specific monoclonal antibodies identify an intermediate state in epsilon protein kinase C activation
AUTHOR: Souroujon Miriam C; Yao Lina; Chen Haibin; Endemann Gerda; Khaner Hanita; Geeraert Virginie; Schechtman Deborah; Gordon Adrienne S; Diamond Ivan; %%%Mochly- Rosen Daria%%% (Reprint
AUTHOR ADDRESS: Sch MedDept Mol Pharmacol, Stanford Univ, Stanford, CA, 94305, USA**USA

AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Journal of Biological Chemistry 279 (17): p17617-17624 April 23, 2004 2004
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Evaluation of the activation state of protein kinase C (PKC) isozymes relies on analysis of subcellular translocation. A monoclonal antibody, 14E6, specific for the activated conformation of epsilonPKC, was raised using the first variable (V1) domain of epsilonPKC as the immunogen. 14E6 binding is specific for epsilonPKC and is greatly increased in the presence of PKC activators. Immunofluorescence staining by 14E6 of neonatal rat primary cardiac myocytes and the NG108-15 neuroblastoma glioma cell line, NG108-15/D2, increases rapidly following cell activation and is localized to new subcellular sites. However, staining of translocated epsilonPKC with 14E6 is transient, and the epitope disappears 30 min after activation of NG-108/15 cells by a D2 receptor agonist. In contrast, subcellular localization associated with activation, as determined by commercially available polyclonal antibodies, persists for at least 30 min. In vitro, epsilonRACK, the receptor for activated epsilonPKC, inhibits 14E6 binding to epsilonPKC, suggesting that the 14E6 epitope is lost or hidden when active epsilonPKC binds to its %%%RACK%%%. Therefore, the 14E6 antibody appears to identify a transient state of activated but non-anchored epsilonPKC. Moreover, binding of 14E6 to epsilonPKC only after activation suggests that lipid-dependent conformational changes associated with epsilonPKC activation precede binding of the activated isozyme to its specific %%%RACK%%%, epsilonRACK. Further, monoclonal antibody 14E6 should be a powerful tool to study the pathways that control rapid translocation of epsilonPKC from cytosolic to membrane localization on activation.

12/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014874636 BIOSIS NO.: 200400243583
Epsilon Protein kinase C (PKC) activation by delta PKC in ethanol-induced cardiac protection from ischemia.
AUTHOR: Inagaki Koichi (Reprint); %%%Mochly-Rosen Daria%%% (Reprint
AUTHOR ADDRESS: Stanford University School of Medicine, Stanford, CA, USA** USA
JOURNAL: Journal of the American College of Cardiology 43 (5 Supplement A): p294A March 3, 2004 2004
MEDIUM: print
CONFERENCE/MEETING: 53rd Annual Scientific Session of the American College of Cardiology New Orleans, LA, USA March 07-10, 2004; 20040307
SPONSOR: American College of Cardiology
ISSN: 0735-1097 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014469191 BIOSIS NO.: 200300424035
Additive protection of the ischemic heart ex vivo by combined treatment with delta-protein kinase C inhibitor and epsilon-protein kinase C activator.
AUTHOR: Inagaki Koichi; Hahn Harvey S; Dorn Gerald W; %%%Mochly-Rosen%%% %%% Daria%%% (Reprint
AUTHOR ADDRESS: Department of Molecular Pharmacology, Stanford University School of Medicine, 269 Campus Dr, CCSR, Room 3145A, Stanford, CA, 94305-5174, USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu

JOURNAL: Circulation 108 (7): p869-875 August 19, 2003 2003
MEDIUM: print
ISSN: 0009-7322 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Protein kinase C (PKC) plays a major role in cardioprotection from ischemia/reperfusion injury. Using an HIV-1 Tat protein-derived peptide to mediate rapid and efficient transmembrane delivery of peptide regulators of PKC translocation and function, we examined the cardioprotective effect of selective delta-PKC inhibitor (deltaV1-1) and epsilon-PKC activator (psiepsilonRACK) peptides for ischemia/reperfusion damage in isolated perfused rat hearts. Furthermore, we examined the protective effects of these PKC isozymes in isolated perfused hearts subjected to ischemia/reperfusion damage using transgenic mice expressing these peptides specifically in their cardiomyocytes. Methods and Results: In isolated perfused rat hearts, administration of deltaV1-1 but not psiepsilonRACK during reperfusion improved cardiac function and decreased creatine phosphokinase release. In contrast, pretreatment with psiepsilonRACK but not deltaV1-1, followed by a 10-minute washout before ischemia/reperfusion, also improved cardiac function and decreased creatine phosphokinase release. Furthermore, administration of psiepsilonRACK before ischemia followed by deltaV1-1 during reperfusion only conferred greater cardioprotective effects than that obtained by each peptide treatment alone. Both the delta-PKC inhibitor and epsilon-PKC activator conferred cardioprotection against ischemia/reperfusion injury in transgenic mice expressing these peptides in the heart, and coexpression of both peptides conferred greater cardioprotective effects than that obtained by the expression of each peptide alone. Conclusions: delta-PKC inhibitor prevents reperfusion injury, and epsilon-PKC activator mimics ischemic preconditioning. Furthermore, treatment with both peptides confers additive cardioprotective effects. Therefore, these peptides mediate cardioprotection by regulating ischemia/reperfusion damage at distinct time points.

12/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014314710 BIOSIS NO.: 200300269243
epsilonPKC IS REQUIRED FOR THE INDUCTION OF TOLERANCE BY ISCHEMIC AND NMDA - MEDIATED PRECONDITIONING.
AUTHOR: Raval A P (Reprint); Dave K R (Reprint); %%%Mochly-Rosen D%%%; Sick T J (Reprint); Lange-Asschenfeldt C (Reprint); Perez-Pinzon M A (Reprint
AUTHOR ADDRESS: CVDRC, Dept Neurol (D4-5), University of Miami School of Medicine, Miami, FL, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 98.5 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102
SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glutamate receptors and calcium have been implicated as triggering factors in the induction of tolerance by ischemic preconditioning (IPC) in the brain. However, little is known about the signal transduction pathway that ensues following this IPC induction. The goals of this study were to determine whether NMDA induce preconditioning via a calcium pathway, promotes translocation of the protein kinase C epsilon (epsilonPKC) isozyme and whether this PKC isozyme is key in the IPC signal transduction pathway. We corroborate here that IPC and a sublethal dose of NMDA were neuroprotective (by 35%; $p<0.05$) against lethal ischemia, whereas blockade of NMDA receptors during IPC diminished IPC-induced neuroprotection. Calcium chelation significantly blocked the protection afforded by both NMDA (by 41%; $p<0.001$) and IPC (by 62%;

p<0.001), suggesting a significant role of Ca2+. Further, neuroprotection was blocked by inhibiting epsilonPKC (using antagonist epsilonV1-2) during IPC (by 124%; p<0.01) and NMDA preconditioning (by 283%; p<0.001), and IPC neuroprotection was emulated with the activator of the epsilonPKC isozyme (psiepsilonRACK) (by 76%; p<0.001). This suggested that epsilonPKC isozyme played a key role in both IPC and NMDA-induced tolerance. The link between NMDA, Ca2+ and epsilonPKC was found when we emulated IPC with the diacyglycerol analogue OAG suggesting an indirect pathway by which Ca2+ could activate the Ca2+-insensitive PKC isozyme. These results demonstrated that the epsilonPKC isozyme played a key role in both IPC and NMDA induced tolerance.

12/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013718649 BIOSIS NO.: 200200312160
psiepsilonRACK, a selective PKCepsilon activating peptide, causes a positive inotropic effect in feline ventricular myocytes
AUTHOR: Harris David M (Reprint); Piacentino Valentino III (Reprint); Chaudhary Khuram (Reprint); %%%Mochly-Rosen Daria%%%; Margulies Kenneth B (Reprint); Houser Steven R (Reprint
AUTHOR ADDRESS: Temple University School of Medicine, 3400 North Broad Street, Philadelphia, PA, 19140, USA**USA
JOURNAL: Biophysical Journal 82 (1 Part 2): p70a January, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 46th Annual Meeting of the Biophysical Society San Francisco, California, USA February 23-27, 2002; 20020223
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013693609 BIOSIS NO.: 200200187120
Molecular dynamics characterization of the C2 domain of protein kinase Cbeta
AUTHOR: Banci Lucia (Reprint); Cavallaro Gabriele; Kheifets Viktoria; %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Centro di Risonanze Magnetiche, University of Florence, Via Luigi Sacconi 6, 50019, Sesto Fiorentino, Florence, Italy**Italy
JOURNAL: Journal of Biological Chemistry 277 (15): p12988-12997 April 12, 2002 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein kinase C (PKC) isozymes comprise a family of related enzymes that play a central role in many intracellular eukaryotic signaling events. Isozyme specificity is mediated by association of each PKC isozyme with specific anchoring proteins, termed RACKs. The C2 domain of betaPKC contains at least part of the %%%RACK%%%-binding sites. Because the C2 domain contains also a %%%RACK%%%-like sequence (termed pseudo-%%%RACK%%%), it was proposed that this pseudo-%%%RACK%%% site mediates intramolecular interaction with one of the %%%RACK%%%-binding sites in the C2 domain itself, stabilizing the inactive conformation of betaPKC. betaPKC depends on calcium for its activation, and the C2 domain contains the calcium-binding sites. The x-ray structure of the C2 domain of betaPKC shows that three Ca2+ ions can be coordinated by two opposing loops at one end of the domain. Starting from this x-ray structure, we have performed molecular dynamics (MD) calculations on the C2 domain of betaPKC bound to three Ca2+ ions, to two Ca2+ ions, and in the Ca2+-free state, in order to analyze the effect of calcium on the %%%RACK%%% -binding sites and the pseudo-%%%RACK%%% sites, as well as on the loops

that constitute the binding site for the Ca2+ ions. The results show that calcium stabilizes the beta-sandwich structure of the C2 domain and thus affects two of the three %%%RACK%%%-binding sites within the C2 domain. Also, the interactions between the third %%%RACK%%%-binding site and the pseudo-%%%RACK%%% site are not notably modified by the removal of Ca2+ ions. On that basis, we predict that the pseudo-%%%RACK%%% site within the C2 domain masks a %%%RACK%%%-binding site in another domain of betaPKC, possibly the V5 domain. Finally, the MD modeling shows that two Ca2+ ions are able to interact with two molecules of O-phospho-L-serine. These data suggest that Ca2+ ions may be directly involved in PKC binding to phosphatidylserine, an acidic lipid located exclusively on the cytoplasmic face of membranes, that is required for PKC activation.

12/7/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013669752 BIOSIS NO.: 200200263263
Selective activation of epsilonPKC protects the intact heart from ischemia/reperfusion arrhythmias
AUTHOR: Restivo Mark (Reprint); Kozhevnikov Dmitry (Reprint); Qu Yongxia (Reprint); %%%Mochly-Rosen Daria%%%; Boutjdir Mohamed
AUTHOR ADDRESS: VA NY Harbor Healthcare System, Brooklyn, NY, USA**USA
JOURNAL: Circulation 104 (17 Supplement): pII.47 October 23, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001; 20011111
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013600152 BIOSIS NO.: 200200193663
Molecular transporters for peptides: Delivery of a cardioprotective epsilonPKC agonist peptide into cells and intact ischemic heart using a transport system, R7
AUTHOR: Chen Leon; Wright Lee R; Chen Che-Hong; Oliver Steven F; Wender Paul A (Reprint); %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA**USA
JOURNAL: Chemistry and Biology (London) 8 (12): p1123-1129 December, 2001 2001
MEDIUM: print
ISSN: 1074-5521
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Recently, we reported a novel oligoguanidine transporter system, polyarginine (R7), which, when conjugated to spectroscopic probes (e.g., fluorescein) and drugs (e.g., cyclosporin A), results in highly water-soluble conjugates that rapidly enter cells and tissues. We report herein the preparation of the first R7 peptide conjugates and a study of their cellular and organ uptake and functional activity. The octapeptide psiepsilonRACK was selected for this study as it is known to exhibit selective epsilon protein kinase C isozyme agonist activity and to reduce ischemia-induced damage in cardiomyocytes. However, psiepsilonRACK is not cell-permeable. Results: Here we show that an R7-psiepsilonRACK conjugate readily enters cardiomyocytes, significantly outperforming psiepsilonRACK conjugates of the transporters derived from HIV Tat and from Antennapedia. Moreover, R7-psiepsilonRACK conjugate reduced ischemic damage when delivered into intact hearts either prior to or after the ischemic insult. Conclusions: Our data suggest that R7 converts a peptide lead into a potential therapeutic

agent for the ischemic heart.

12/7/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013342190 BIOSIS NO.: 200100514029
Adaptor proteins in protein kinase C-mediated signal transduction
AUTHOR: Schechtman Deborah; %%%Mochly-Rosen Daria%%% (Reprint
AUTHOR ADDRESS: Department of Molecular Pharmacology, School of Medicine, Stanford University, 269 Campus Drive, CCSR 3145, Stanford, CA, 94305-5174, USA**USA
JOURNAL: Oncogene 20 (44): p6339-6347 1 October, 2001 2001
MEDIUM: print
ISSN: 0950-9232
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Spatial and temporal organization of signal transduction is essential in determining the speed and precision by which signaling events occur. Adaptor proteins are key to organizing signaling enzymes near their select substrates and away from others in order to optimize precision and speed of response. Here, we describe the role of adaptor proteins in determining the specific function of individual protein kinase C (PKC) isozymes. These isozyme-selective proteins were called collectively RACKs (receptors for activated C-kinase). The role of RACKs in PKC-mediated signaling was determined using isozyme-specific inhibitors and activators of the binding of each isozyme to its respective %%%RACK%%%. In addition to anchoring activated PKC isozymes, RACKs anchor other signaling enzymes. RACK1, the anchoring protein for activated betaIIPKC, binds for example, Src tyrosine kinase, integrin, and phosphodiesterase. RACK2, the epsilonPKC-specific %%%RACK%%%, is a coated-vesicle protein and thus is involved in vesicular release and cell-cell communication. Therefore, RACKs are not only adaptors for PKC, but also serve as adaptor proteins for several other signaling enzymes. Because at least some of the proteins that bind to RACKs, including PKC itself, regulate cell growth, modulating their interactions with RACKs may help elucidate signaling pathways leading to carcinogenesis and could result in the identification of novel therapeutic targets.

12/7/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012863703 BIOSIS NO.: 200100035542
Distortion of cardiomyocyte ultrastructure and lethal heart failure from in-vivo PKC delta inhibition
AUTHOR: Hahn Harvey S (Reprint); Wu Guangyu (Reprint); Jantz Tamara (Reprint); Boivin Gregory P (Reprint); Lorenz John N (Reprint); %%%Mochly-Rosen Daria%%%; Dorn Gerald W
AUTHOR ADDRESS: Univ of Cincinnati, Cincinnati, OH, USA**USA
JOURNAL: Circulation 102 (18 Supplement): pII.160 October 31, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: Abstracts from American Heart Association Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000; 20001112
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012625258 BIOSIS NO.: 200000343571
Cardiotrophic effects of protein kinase C epsilon: Analysis by in vivo

modulation of PKCepsilon translocation
AUTHOR: %%%Mochly-Rosen Daria%%%; Wu Guangyu; Hahn Harvey; Osinska Hanna; Liron Tamar; Lorenz John N; Yatani Atsuko; Robbins Jeffrey; Dorn Gerald W II (Reprint
AUTHOR ADDRESS: Division of Cardiology, University of Cincinnati Medical Center, 231 Bethesda Ave, Cincinnati, OH, 45267-0542, USA**USA
JOURNAL: Circulation Research 86 (11): p1173-1179 June 9, 2000 2000
MEDIUM: print
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein kinase C (PKC) is a key mediator of many diverse physiological and pathological responses. Although little is known about the specific in vivo roles of the various cardiac PKC isozymes, activation-induced translocation of PKC is believed to be the primary determinant of isozyme-specific functions. Recently, we have identified a catalytically inactive peptide translocation inhibitor (epsilonV1) and translocation activator (psiepsilonRACK (receptors for activated C kinase)) specifically targeting PKCepsilon. Using cardiomyocyte-specific transgenic expression of these peptides, we combined loss- and gain-of-function approaches to elucidate the in vivo consequences of myocardial PKCepsilon signaling. As expected for a PKCepsilon %%%RACK%%% binding peptide, confocal microscopy showed that epsilonV1 decorated cross-striated elements and intercalated disks of cardiac myocytes. Inhibition of cardiomyocyte PKCepsilon by epsilonV1 at lower expression levels upregulated alpha-skeletal actin gene expression, increased cardiomyocyte cell size, and modestly impaired left ventricular fractional shortening. At high expression levels, epsilonV1 caused a lethal dilated cardiomyopathy. In contrast, enhancement of PKCepsilon translocation with psiepsilonRACK resulted in selectively increased beta myosin heavy chain gene expression and normally functioning concentric ventricular remodeling with decreased cardiomyocyte size. These results identify for the first time a role for PKCepsilon signaling in normal postnatal maturational myocardial development and suggest the potential for PKCepsilon activators to stimulate "physiological" cardiomyocyte growth.

12/7/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012305935 BIOSIS NO.: 200000024248
Attenuation of cardiac growth in transgenic mice expressing the PKCepsilon inhibitory epsilonV1 peptide
AUTHOR: Wu Guangyu (Reprint); Wang Ying (Reprint); Jantz Tamara (Reprint); Canning Amy M (Reprint); Robbins Jeffrey; %%%Mochly-Rosen Daria%%%; Dorn Gerald W II
AUTHOR ADDRESS: Univ of Cincinnati, Cincinnati, OH, USA**USA
JOURNAL: Circulation 100 (18 SUPPL.): pI.53 Nov. 2, 1999 1999
MEDIUM: print
CONFERENCE/MEETING: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999; 19991107
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012305934 BIOSIS NO.: 200000024247
Hypertrophic effects of PKCepsilon activation in transgenic mice expressing the PKCepsilon pseudo-%%%RACK%%% peptide
AUTHOR: Wu Guangyu (Reprint); Canning Amy M (Reprint); Jantz Tamara (Reprint); %%%Mochly-Rosen Daria%%%; Dorn Gerald W II
AUTHOR ADDRESS: Univ of Cincinnati, Cincinnati, OH, USA**USA

JOURNAL: Circulation 100 (18 SUPPL.): pI.53 Nov. 2, 1999 1999
MEDIUM: print
CONFERENCE/MEETING: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999; 19991107
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012293921 BIOSIS NO.: 200000012234
Protein kinase C-epsilon is responsible for the protection of preconditioning in rabbit cardiomyocytes
AUTHOR: Liu Guang S; Cohen Michael V; %%%Mochly-Rosen Daria%%%; Downey James M (Reprint
AUTHOR ADDRESS: Department of Physiology, College of Medicine, University of South Alabama, Mobile, AL, 36688-0002, USA**USA
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (10): p1937-1948 Oct., 1999 1999
MEDIUM: print
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The role of protein kinase C (PKC) in the protection of ischemic preconditioning (PC) is still controversial, partly because of the multiple isozymes of PKC and the inability to directly measure PKC activity in vivo. In this study we have used novel peptide inhibitors which correspond to part of the amino acid sequence from the isozyme-specific %%%RACK%%%-binding site on the PKC molecule. The peptides prevent binding of a specific activated PKC isozyme to its %%%RACK%%%, thus halting isozyme translocation and function. The inhibitor peptides are cross-linked to the membrane-translocating antennapedia homeodomain peptide that allows their entry into cells. The effect of inhibitors of PKC-beta, -delta, -epsilon and -eta were evaluated. Rabbit adult ventricular myocytes were obtained by enzymatic dissociation. Ischemia was simulated by centrifuging the myocytes into an oxygen-free pellet for 180 min. PC was induced by 10 min of pelleting followed by resuspension in oxygenated medium for 15 min. During simulat ed ischemia cells undergo a predictable increase in osmotic fragility as judged by determination of the number of stained cells following their incubation in hypotonic (85 mOsm) trypan blue. The percentage of cells experiencing membrane rupture, and thus cell staining, was considered to be an index of ischemic injury. PC significantly delayed the progression of osmotic fragility during simulated ischemia ($P<0.01$). The protection of PC was abolished by the peptide inhibitor of PKC-epsilon but not by the peptide inhibitors selective for PKC-beta, PKC-delta, or PKC-eta; each was applied at 100 nM. Protection could also be induced by the PKC activator oleoylacetyl glycerol, and that protection was aborted by the inhibitor selective for PKC-epsilon, but not by the inhibitor for PKC-delta. None of the above peptide treatments affected the osmotic fragility in non-PC cells during simulated ischemia. Our studies further support PKC as a critical part of the signal transduction pathway in PC and indicate that P KC-epsilon alone is responsible for the early phase of PC's protection in rabbit cardiomyocytes.

12/7/25 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011233865 BIOSIS NO.: 199800028112
The coatomer protein beta'-COP, a selective binding protein (%%%RACK%%%) for protein kinase Cepsilon
AUTHOR: Csukai Michael; Chen Che-Hong; De Matteis Maria Antonietta; %%%Mochly-Rosen Daria%%% (Reprint

AUTHOR ADDRESS: Dep. Molecular Pharmacol., Stanford Univ. Sch. Med., Stanford, CA 94305-5332, USA**USA
JOURNAL: Journal of Biological Chemistry 272 (46): p29200-29206 Nov. 14, 1997 1997
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Distinct subcellular localization of activated protein kinase C (PKC) isozymes is mediated by their binding to isozyme-specific RACKs (receptors for activated C-kinase). Our laboratory has previously isolated one such protein, RACK1, and demonstrated that this protein displays specificity for PKCbeta. We have recently shown that at least part of the PKCepsilon %%%RACK%%%-binding site on PKCepsilon lies within the unique V1 region of this isozyme (Johnson, J. A., Gray, M. O., Chen, C.-H., and Mochly-Rosen, D. (1996) J. Biol. Chem. 271, 24962-24966). Here, we have used the PKCepsilon V1 region to clone a PKCepsilon-selective %%%RACK%%%, which was identified as the COPI coatomer protein, beta'-COP. Similar to RACK1, beta'-COP contains seven repeats of the WD40 motif and fulfills the criteria previously established for RACKs. Activated PKCepsilon colocalizes with beta'-COP in cardiac myocytes and binds to Golgi membranes in a beta'-COP-dependent manner. A role for PKC in control of secretion has been previously suggested, but this is the first report of direct protein/protein interaction of PKCepsilon with a protein involved in vesicular trafficking.

12/7/26 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011086338 BIOSIS NO.: 199799720398
RACK1, a protein kinase C receptor protein, coordinates binding of pleckstrin homology domains and activated protein kinase C
AUTHOR: Rodriguez M M (Reprint); Ron D (Reprint); Touhara K; Chen C-H (Reprint); %%%Mochly-Rosen D%%% (Reprint
AUTHOR ADDRESS: Stanford Univ. Sch. Med., Stanford, CA, USA**USA
JOURNAL: FASEB Journal 11 (9): pA1187 1997 1997
CONFERENCE/MEETING: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997; 19970824
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/27 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011086337 BIOSIS NO.: 199799720397
Beta-COP: A COPI coatomer protein is also an epsilon protein kinase C specific %%%rack%%%
AUTHOR: Csukai M; Chen C-H; %%%Mochly-Rosen D%%%
AUTHOR ADDRESS: Stanford Univ. Medical Sch., Stanford, CA 94305, USA**USA
JOURNAL: FASEB Journal 11 (9): pA1187 1997 1997
CONFERENCE/MEETING: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997; 19970824
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

12/7/28 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010773839 BIOSIS NO.: 199799407899
Translocation inhibitors define specificity of protein kinase C isoenzymes in pancreatic beta-cells
AUTHOR: Yedovitzky Michael; %%%Mochly-Rosen Daria%%%; Johnson John A; Gray Mary O; Ron Dorit; Abramovitch Eva; Cerasi Erol; Nesher Rafael (Reprint
AUTHOR ADDRESS: Dep. Endocrinol. Metabolism, Hadassah Univ. Hosp., PO Box 12000, 91120 Jerusalem, Israel**Israel
JOURNAL: Journal of Biological Chemistry 272 (3): p1417-1420 1997 1997
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The protein kinase C (PKC) family consists of 11 isoenzymes. Following activation, each isoenzyme translocates and binds to a specific receptor for activated C kinase (%%%RACK%%%) (Mochly-Rosen, D. (1995) Science 268, 247-251) that provides an anchoring site in close proximity to the isoenzyme's specific substrate. Pancreatic islet cells contain at least six PKC isoenzymes (Knutson, K. L., and Hoenig, M. (1994) Endocrinology 135,881-886). Although PKC activation enhances insulin release, the specific function of each isoenzyme is unknown. Here we show that following stimulation with glucose, alpha-PKC and epsilon-PKC translocate to the cell's periphery, while delta-PKC and zeta-PKC translocate to perinuclear sites. beta-C2-4, a peptide derived from the RACK1-binding site in the C2 domain of beta-PKC, inhibits translocation of alpha-PKC and reduces insulin response to glucose. Likewise, epsilon-V1-2, an epsilon-PKC-derived peptide containing the site for its specific %%%RACK%%%, inhibits translocation of epsilon-PKC and reduces insulin response to glucose. Inhibition of islet-glucose metabolism with mannoheptulose blocks translocation of both alpha-PKC and epsilon-PKC and diminishes insulin response to glucose while calcium-free buffer inhibits translocation of alpha-PKC but not epsilon-PKC and lowers insulin response by 50%. These findings illustrate the unique ability of specific translocation inhibitors to elucidate the isoenzyme-specific functions of PKC in complex signal transduction pathways.

12/7/29 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010078737 BIOSIS NO.: 199598546570
C2 region-derived peptides inhibit translocation and function of beta protein kinase C in vivo
AUTHOR: Ron Dorit; Luo Jianhua; %%%Mochly-Rosen Daria%%% (Reprint
AUTHOR ADDRESS: Dep. Mol. Pharmacol., Sch. Med., Stanford University, Stanford, CA 94305-5332, USA**USA
JOURNAL: Journal of Biological Chemistry 270 (41): p24180-24187 1995 1995
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: RACK1 is a protein kinase C (PKC)-binding protein that fulfills the criteria previously established for a receptor for activated C-kinase (%%%RACK%%%). If binding of PKC to %%%RACK%%% anchors the activated enzyme near its protein substrates, then inhibition of this binding should inhibit translocation and function of the enzyme in vivo. Here, we have identified such inhibitors that mimic the RACK1-binding site on beta-PKC. We first found that a C2-containing fragment, but not a C1-containing fragment of beta-PKC, bound to RACK1 and inhibited subsequent beta-PKC binding. The RACK1-binding site was further mapped; peptides beta-C2-1 (beta-PKC(209-216)), beta-C2-2 (beta-PKC(186-198)), and beta-C2-4 (beta-PKC(218-226), but not a number of control peptides, bound to RACK1 and inhibited the C2 fragment binding to RACK1. Peptides beta-C2-1, beta-C2-2, and beta-C2-4 specifically inhibited phorbol ester-induced translocation of the C2-containing isozymes in cardiac

myocytes and insulin-induced beta-PKC translocation and function in Xenopus oocytes. Therefore, peptides corresponding to amino acids 186-198, and 209-226 within the C2 region of the beta-PKC are specific inhibitors for functions mediated by beta-PKC.

12/7/30 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009652768 BIOSIS NO.: 199598120601
An autoregulatory region in protein kinase C: The pseudoanchoring site
AUTHOR: Ron Dorit; %%%Mochly-Rosen Daria%%% (Reprint
AUTHOR ADDRESS: Dep. Mol. Pharmacol., Stanford Univ., Sch. Medicine, Stanford, CA 94305-5332, USA**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 92 (2): p492-496 1995 1995
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have previously identified receptors for activated C kinase (RACKs) as components of protein kinase C (PKC) signaling. RACK1, a recently cloned 36-kDa %%%RACK%%%, has short sequences of homology to PKC. A possible explanation for the homologous sequences between the ligand (PKC) and its intracellular receptor (RACK1) may be that, similar to the pseudosubstrate autoregulatory sequence on PKC, there is also a pseudo-RACK1 binding site on the enzyme. If this is the case, peptides with these sequences (derived from either RACK1 or PKC) are expected to affect PKC binding to RACK1 in vitro and PKC-mediated functions in vivo. Here, we show that the PKC-derived peptide (pseudoRACK1 peptide), but not its RACK1 homologue, modulated PKC function both in vitro and in vivo. Our data suggest that the pseudo-RACK1 peptide binds and activates PKC in the absence of PKC activators and thereby acts as an agonist of PKC function in vivo. Therefore, the pseudo-RACK1 sequence in PKC appears to be another autoregulatory site; when PKC is in an inactive conformation, the pseudo-RACK1 site interacts with the %%%RACK%%%-binding site. Activation of PKC exposes the %%%RACK%%%-binding site, enabling the association of the enzyme with its anchoring %%%RACK%%%. Similar pseudoanchoring sites may regulate the function of other protein kinases.

12/7/31 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008428761 BIOSIS NO.: 199294130602
P65 FRAGMENTS HOMOLOGOUS TO THE C2 REGION OF PROTEIN KINASE C BIND TO THE INTRACELLULAR RECEPTORS FOR PROTEIN KINASE C
AUTHOR: %%%MOCHLY-ROSEN D%%% (Reprint); MILLER K G; SCHELLER R H; KHANER H; LOPEZ J; SMITH B L
AUTHOR ADDRESS: ERNEST GALLO CLIN RES CENT, BUILDING 1, ROOM 101, SAN FRANCISCO GENERAL HOSP, SAN FRANCISCO, CALIF 94110, USA**USA
JOURNAL: Biochemistry 31 (35): p8120-8124 1992
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Receptors for activated protein kinase C (RACKs) have been isolated from the particulate cell fraction of heart and brain. We previously demonstrated that binding of protein kinase C (PKC) to RACKs requires PKC activators and is via a site on PKC that is distinct from the substrate binding site. Here, we examine the possibility that the C2 region in the regulatory domain of PKC is involved in binding of PKC to RACKs. The synaptic vesicle-specific p65 protein contains two regions homologous to the C2 region of PKC. We found that three p65 fragments, containing either one or two of these PKC C2 homologous regions, bound to highly purified RACKs. Binding of the p65 fragments and PKC to RACKs was mutually exclusive; preincubation of RACKs with the p65 fragments

inhibited PKC binding, and preincubation of RACKs with PKC inhibited binding of the p65 fragments. Preincubation of the p65 fragments with a peptide resembling the PKC binding site on RACKs also inhibited p65 binding to RACKs, suggesting that PKC and p65 bind to the same or nearby regions on RACKs. Since the only homologous region between PKC and the p65 fragments is the C2 region, these results suggest that the C2 region on PKC contains at least part of the %%%RACK%%% binding site.

12/7/32 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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18788361 PMID: 15894568
PKC-{varepsilon}-dependent survival signals in diabetic hearts.
Malhotra Ashwani; Begley Rebecca; Kang Barinder P S; Rana Irmindra; Liu Jing; Yang Guiping; %%%Mochly-Rosen Daria%%%; Meggs Leonard G
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American journal of physiology. Heart and circulatory physiology (United States) Oct 2005, 289 (4) pH1343-50, ISSN 0363-6135 Journal Code: 100901228
Contract/Grant No.: AG-014121; AG; NIA; HL-59139; HL; NHLBI; HL-69020; HL; NHLBI
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Diabetes mellitus is complicated by the development of a primary cardiomyopathy, which contributes to the excess morbidity and mortality of this disorder. The protein kinase C (PKC) family of isozymes plays a key role in the cardiac phenotype expressed during postnatal development and in response to pathological stimuli. Hyperglycemia is an activating signal for cardiac PKC isozymes that modulate a myriad of cell events including cell death and survival. The epsilon-isozyme of the PKC family transmits a powerful survival signal in cardiac muscle cells. Accordingly, to test the hypothesis that endogenous activation of cardiac PKC-epsilon will protect against hyperglycemic cell injury and left ventricular dysfunction, diabetes mellitus was induced using streptozotocin in genetically engineered mice with cardiac-specific expression of the PKC-epsilon translocation activator [psiepsilon-receptors for activated C kinase (psiepsilon-%%%RACK%%%)]. The results demonstrate a striking PKC-epsilon cardioprotective phenotype in diabetic psiepsilon-%%%RACK%%% (epsilon-agonist) mice that is characterized by inhibition of the hyperglycemia apoptosis signal, attenuation of hyperglycemia-mediated oxidative stress, and preservation of parameters of left ventricular pump function. Hearts of diabetic epsilon-agonist mice exhibited selective trafficking of PKC-epsilon to membrane and mitochondrial compartments, phosphorylation/inactivation of the mitochondrial Bad protein, and inhibition of cytochrome c release. We conclude that activation of endogenous PKC-epsilon in hearts of diabetic epsilon-agonist mice promotes the survival phenotype, attenuates markers of oxidative stress, and inhibits the negative inotropic properties of chronic hyperglycemia.
Record Date Created: 20050915
Record Date Completed: 20051024
Date of Electronic Publication: 20050513

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13/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0015621854 BIOSIS NO.: 200510316354
Activated E-protein kinase C accelerates the transition from compensatory left ventricular hypertrophy to heart failure in hypertensive rats
AUTHOR: Inagaki Koichi (Reprint); Begley Rebecca; %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94305 USA**USA
JOURNAL: Circulation 110 (17, Suppl. S): p598 OCT 26 2004 2004

CONFERENCE/MEETING: 77th Scientific Meeting of the
American-Heart-Association New Orleans, LA, USA November 07 -10, 2004;
20041107
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: We have previously demonstrated that epsilon protein kinase C (epsilon PKC) levels are increased in compensatory hypertrophied left ventricle (LV) in Dahl salt-sensitive rats with systemic hypertension, and the activation of epsilon PKC induces the physiological LV hypertrophy without impaired cardiac function in transgenic mice expressing the epsilon PKC selective activator peptice (Psi epsilon %%%RACK%%%). Hypothesis: Here, we hypothesized that epsilon PKC signaling is necessary to maintain compensatory hypertrophy and thus the treatment with IVERACK should prevents the progression of heart failure. Methods: Dahl salt-sensitive rats were fed with 8% salt diet from 6 weeks old to induce systemic hypertension. Dahl salt-sensitive rats were treated continuously with Psi epsilon %%%RACK%%% (n=15) or with control carrier peptice Tat (n=12) from 15 to 17 weeks old using subcutaneously implanted osmotic pump. Cardiac function was determined by echocardiography. Results: The treatment with Psi epsilon %%%RACK%%% before the transition to heart failure shortened the survival rate (Psi epsilon %%%RACK%%% 118.9 +/- 2.8 vs. control 138.5 +/- 10.3 days old, P<0.05). In addition, the treatment with Psi epsilon %%%RACK%%% resulted in reduced fractional shortening (Psi epsilon %%%RACK%%% 35.9 +/- 3.3 vs. control 46.5 +/- 2.6 %, P<0.05), increased LV end diastolic dimension (Psi epsilon %%%RACK%%% 8.3 +/- 0.4 vs. control 7.5 +/- 0.2 mm, P<0.05), increased systolic wall stress (Psi epsilon %%%RACK%%% 139.0 +/- 25.4 vs. control 85.3 +/- 7.2 g/cm(2), P<0.05), and increased LV weight (Psi epsilon %%%RACK%%% 1.38 +/- 0.05 vs. control 1.22 +/- 0.04 g, P<0.05) and lung weight (Psi epsilon %%%RACK%%% 3.28 +/- 0.98 vs. control 1.73 +/- 0.1 g, P<0.05) as compared with the treatment with the control peptice at 17 weeks old. There were no significant differences between the two groups in systolic blood pressure (Psi epsilon %%%RACK%%% 255.2 +/- 7.9 vs. control 247.9 +/- 4.7 mmHg) and in body weight (Psi epsilon %%%RACK%%% 345.4 +/- 16.4 vs. control 354.2 +/- 13.0 g). Conclusion: Continuous activation of epsilon PKC in hypertrophied LV myocardium of hypertensive rats induces further myocardial hypertrophy, but accelerates the transition to heart failure in contrast to our initial hypothesis.

13/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015619212 BIOSIS NO.: 200510313712
An E-PKC activator reduces ventricular fibrillation, and a Delta-PKC inhibitor prevents stunning in a porcine model of acute myocardial infarction
AUTHOR: Inagaki Koichi (Reprint); Ikeno Fumiaki; %%%Mochly-Rosen Dana%%%
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94305 USA**USA
JOURNAL: Circulation 110 (17, Suppl. S): p28 OCT 26 2004 2004
CONFERENCE/MEETING: 77th Scientific Meeting of the
American-Heart-Association New Orleans, LA, USA November 07 -10, 2004;
20041107
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: Previous studies have demonstrated that an epsilon protein kinase C (PKC)-selective activator peptide (psi epsilon %%%RACK%%%) mimics ischemic preconditioning and a delta PKC-selective inhibitor peptide (delta V1-1) prevents reperfusion injury in an isolated perfused rat heart model or in a porcine model. Hypothesis: Here, we hypothesized that the combined treatment with these PKC regulators enhances cardioprotection in an in vivo porcine heart model of acute

myocardial infarction. Methods: The left anterior descending artery (LAD) was occluded for 30 minutes using a balloon catheter. psi epsilon %%%RACK%%% was injected to the ischemic area through the lumen of the balloon catheter during the first 10 minutes of ischemia. delta V1-1 was injected to ischemic area during the last 1 minute of ischemia (n=12-16 for each group). Results: The treatment with either psi epsilon %%%RACK%%% or delta V1-1 reduced infarct size by similar to 70% in the similar level as compared with control. psi epsilon %%%RACK%%%, but not delta V1-1, reduced the incidence of ventricular fibrillation (VF) during ischemia/reperfusion. In contrast, delta V1-1, but not psi epsilon %%%RACK%%%, improved cardiac function immediately after reperfusion. Furthermore, when psi epsilon %%%RACK%%% was injected for the first 10 minutes of ischemia followed by delta V1-1 injection for the last 1 minute of ischemia, this combined treatment with delta V1-1 and psi epsilon %%%RACK%%% further reduced infarct size (control, 32.3 +/- 2.4%, psi epsilon %%%RACK%%%; 13.9 +/- 1.4%, delta V1-1; 9.3 +/- 1.1%, combined treatment; 4.5 +/- 1.4%; P<0.05 as compared with control, psi epsilon %%%RACK%%% or delta V1-1, alone), The combined treatment also reduced the incidence of VF during ischemia/reperfusion (control; 88%, psi epsilon %%%RACK%%%; 25%, delta V1-1. 64%, combined treatment; 38%; P<0.05 as compared with control or delta V1-1 alone) and improved ejection fraction immediately after reperfusion (control; 38.3 +/- 2.9%, psi epsilon %%%RACK%%%; 42.5 +/- 3.7%, delta V1-1; 48.4 +/- 3.7%, combined treatment; 53.2 +/- 1.7%; P<0.05 as compared with control or psi epsilon %%%RACK%%% alone). Conclusion: An epsilon PKC activator reduced the incidence of VF, a delta PKC inhibitor prevented cardiac stunning, and the combined treatment with these PKC regulators conferred additive beneficial effects in cardiac damage, arrhythmia and cardiac function. Thus, the combined treatment with an epsilon PKC activator and a delta PKC inhibitor may be useful for the treatment of acute myocardial infarction.

13/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015616842 BIOSIS NO.: 200510311342
PKC-epsilon-dependent survival signals in diabetic hearts
AUTHOR: Malhotra Ashwani (Reprint); Begley Rebecca; Kang Barinder P S; Rana Irmindra; Liu Jing; Yang Guiping; %%%Mochly-Rosen Daria%%%; Meggs Leonard G
AUTHOR ADDRESS: Univ Med and Dent New Jersey, New Jersey Med Sch, Dept Med, Div Nephrol and Hypertens, MSB I-524, 185 S Orange Ave, Newark, NJ 07103 USA**USA
AUTHOR E-MAIL ADDRESS: Malhotas@umdnj.edu
JOURNAL: American Journal of Physiology - Heart and Circulatory Physiology 289 (4): pH1343-H1350 OCT 2005 2005
ISSN: 0363-6135
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Diabetes mellitus is complicated by the development of a primary cardiomyopathy, which contributes to the excess morbidity and mortality of this disorder. The protein kinase C (PKC) family of isozymes plays a key role in the cardiac phenotype expressed during postnatal development and in response to pathological stimuli. Hyperglycemia is an activating signal for cardiac PKC isozymes that modulate a myriad of cell events including cell death and survival. The epsilon-isozyme of the PKC family transmits a powerful survival signal in cardiac muscle cells. Accordingly, to test the hypothesis that endogenous activation of cardiac PKC-epsilon will protect against hyperglycemic cell injury and left ventricular dysfunction, diabetes mellitus was induced using streptozotocin in genetically engineered mice with cardiac-specific expression of the PKC-epsilon translocation activator [psi epsilon-receptors for activated C kinase (psi epsilon-%%%RACK%%%)]. The results demonstrate a striking PKC-epsilon cardioprotective phenotype in diabetic psi epsilon-%%%RACK%%% (epsilon-agonist) mice that is characterized by inhibition of the hyperglycemia apoptosis signal, attenuation of hyperglycemia-mediated oxidative stress, and preservation of parameters of left ventricular pump function. Hearts of diabetic

epsilon-agonist mice exhibited selective trafficking of PKC-epsilon to membrane and mitochondrial compartments, phosphorylation/inactivation of the mitochondrial Bad protein, and inhibition of cytochrome c release. We conclude that activation of endogenous PKC-epsilon in hearts of diabetic epsilon-agonist mice promotes the survival phenotype, attenuates markers of oxidative stress, and inhibits the negative inotropic properties of chronic hyperglycemia.

13/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015544562 BIOSIS NO.: 200510239062
delta PKC-mediated activation of epsilon PKC in ethanol-induced cardiac protection from ischemia
AUTHOR: Inagaki K; %%%Mochly-Rosen D%%% (Reprint
AUTHOR ADDRESS: Stanford Univ, Sch Med, Dept Mol Pharmacol, CCSR, Room 3145A,269 Campus Dr, Stanford, CA 94305 USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Journal of Molecular and Cellular Cardiology 39 (2): p203-211 AUG 2005 2005
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous studies have demonstrated that acute ethanol exposure induces activation of 6 protein kinase C (delta PKC) and epsilon PKC, and mimics ischemic preconditioning via epsilon PKC activation. However, the role of delta PKC isozyme in ischemia and reperfusion is still controversial. Here, we investigated the role of delta PKC in ethanol-induced cardioprotection using a selective delta PKC activator (psi delta %%%RACK%%%), or inhibitor (delta V1-1), and a selective epsilon PKC inhibitor (epsilon V1-2) in isolated mouse hearts. Mice were injected intraperitoneally or by gavage with ethanol, regulators of 6 and epsilon PKC or an adenosine A, receptor blocker (DPCPX). Isolated perfused mouse hearts were subjected to a 30-min global ischemia and a 120-min reperfusion, ex vivo. Injection of 0.5 g/kg ethanol 1 h, but not 10 min, before ischemia reduced infarct size and CPK release. Pretreatment with epsilon V1-2 abolished this ethanol-induced cardioprotection. Pretreatment with delta V1-1 induced cardioprotection when injected with ethanol (0.5 g/kg) 10 min before ischemia, but delta V1-1 partly inhibited ethanol-induced cardioprotection when injected with ethanol 1-h before the onset of ischemia. psi delta %%%RACK%%% injection 1 h, but not 10 min, before ischemia induced cardioprotection and translocation of epsilon PKC from the cytosol to the particulate fraction. Pretreatment with DPCPX or epsilon V1-2 inhibited psi delta %%%RACK%%%-induced cardioprotection and translocation of epsilon PKC. Therefore, activation of epsilon PKC-induced by ethanol or by the delta PKC activator is cardioprotective, provided that sufficient time passes to allow delta PKC-induced activation of epsilon PKC, an A(1) adenosine receptor-dependent process. (c) 2005 Published by Elsevier Ltd.

13/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015518955 BIOSIS NO.: 200510213455
A critical role of mitochondrial aldehyde dehydrogenase in ethanol-induced ePKC-mediated cardioprotection against ischemia/reperfusion damage
AUTHOR: Chen C-H (Reprint); Inagaki K; %%%Mochly-Rosen D%%%
AUTHOR ADDRESS: Stanford Univ, Dept Mol Pharmacol, Stanford, CA 94305 USA** USA
JOURNAL: Alcoholism Clinical and Experimental Research 28 (5, Suppl. S): p 54A MAY 2004 2004
CONFERENCE/MEETING: 27th Annual Meeting of the Research-Society-on-Alcoholism Vancouver, CANADA June 26 -30, 2004; 20040626
SPONSOR: Res Soc Alcoholism

ISSN: 0145-6008
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0015491583 BIOSIS NO.: 200510186083
Mechanism of interaction between Annexin V and delta PKC
AUTHOR: Kheifets Viktoria (Reprint); Bright Rachel; Wong Melissa; Kihara Yasuki; %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Stanford Univ, Sch Med, Stanford, CA 94205 USA**USA
JOURNAL: FASEB Journal 18 (8, Suppl. S): pC213 MAY 14 2004 2004
CONFERENCE/MEETING: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology Boston, MA, USA June 12 -16, 2004; 20040612
SPONSOR: Amer Soc BioChem & Mol Biol
Int Union Biochem & Mol Biol
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Annexins form a family of calcium-dependent membrane-binding proteins. At present, 13 members of the family have been identified. The physiological role of these highly abundant cytosolic proteins is currently not known. However, a number of links exist between the annexins and the protein kinase C family that consists of at least I I members, exhibiting isozyme-specific localization, translocation, and functional profiles. Annexins associate with PKC isozymes; some are substrates of specific PKC isozymes, whereas others are inhibitors. Activation of PKC and its subsequent translocation to the cell membrane results in protection of the heart from myocardial ischemia. JTV519, a benzothiazepine derivative, protects hearts from ischemic injury and from Ca2+ overload-induced myocardial injury. JTV519 binds tightly to annexin V and is thought to confer its protective effect through this interaction. In addition, JTV519 treatment of cardiac myocytes causes translocation of delta PKC to the cell membrane. Furthermore, Annexin V contains a sequence that closely resembles a sequence found on delta PKC in a location that has previously been found to be involved in inhibitory intramolecular interaction, the pseudo-%%%RACK%%% site. In this study,we investigate the exact mechanism of interaction between annexin V and deltaPKC. We show that the interaction occurs through the VI domain of delta PKC in an isozyme-selective manner using both overlay and pulldown assays. We also show that peptides that most closely resemble the annexin V sequence bind to delta PKC. Co-immunoprecipitation studies from neonatal cardiac myocytes show that annexin V and delta PKC interaction is dependent on cell activation state.Together, these studies indicate a mechanism for both the interaction of annexin V and delta PKC as well as the mechanism for the protection of the heart by both a delta PKC activator and JTV519.

13/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0015186866 BIOSIS NO.: 200500092779
Cardioprotection by epsilon-protein kinase C activation from ischemia - Continuous delivery and antiarrhythmic effect of an epsilon-protein kinase C-activating peptide
AUTHOR: Inagaki Koichi; Begley Rebecca; Ikeno Fumiaki; %%%Mochly-Rosen%%% %%% Daria%%% (Reprint
AUTHOR ADDRESS: Sch MedDept Mol Pharmacol, Stanford Univ, 269 Campus Dr,3145 CCSR, Stanford, CA, 94305, USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Circulation 111 (1): p44-50 January 4, 2005 2005

MEDIUM: print
ISSN: 0009-7322 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background - We previously showed that a selective activator peptide of epsilon-protein kinase C (PKC), psiepsilonRACK, conferred cardioprotection against ischemia-reperfusion when delivered ex vivo before the ischemic event. Here, we tested whether in vivo continuous systemic delivery of psiepsilonRACK confers sustained cardioprotection against ischemia-reperfusion in isolated mouse hearts and whether psiepsilonRACK treatment reduces infarct size or lethal arrhythmias in porcine hearts in vivo. Methods and Results - After psiepsilonRACK was systemically administered in mice either acutely or continuously, hearts were subjected to ischemia-reperfusion in an isolated perfused model. Whereas psiepsilonRACK-induced cardioprotection lasted 1 hour after a single intraperitoneal injection, continuous treatment with psiepsilonRACK induced a sustained preconditioned state during the 10 days of delivery. There was no desensitization to the therapeutic effect, no downregulation of epsilonPKC, and no adverse effects after sustained psiepsilonRACK delivery. Porcine hearts were subjected to ischemia-reperfusion in vivo, and psiepsilonRACK was administered by intracoronary injection during the first 10 minutes of ischemia. psiepsilonRACK treatment reduced infarct size (34+/-2% versus 14+/-1%, control versus psiepsilonRACK) and resulted in fewer cases of ventricular fibrillation during ischemia-reperfusion (87.5% versus 50%, control versus psiepsilonRACK). Conclusions - The epsilonPKCactivator psiepsilonRACK induced cardioprotection both in vivo and ex vivo, reduced the incidence of lethal arrhythmia during ischemia-reperfusion, and did not cause desensitization or downregulation of epsilonPKC after sustained delivery. Thus, psiepsilonRACK may be useful for patients with ischemic heart disease. In addition, the psiepsilonRACK peptide should be a useful pharmacological agent for animal studies in which systemic and sustained modulation of epsilonPKC in vivo is needed.

13/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014874636 BIOSIS NO.: 200400243583
Epsilon Protein kinase C (PKC) activation by delta PKC in ethanol-induced cardiac protection from ischemia.
AUTHOR: Inagaki Koichi (Reprint); %%%Mochly-Rosen Daria%%% (Reprint
AUTHOR ADDRESS: Stanford University School of Medicine, Stanford, CA, USA** USA
JOURNAL: Journal of the American College of Cardiology 43 (5 Supplement A): p294A March 3, 2004 2004
MEDIUM: print
CONFERENCE/MEETING: 53rd Annual Scientific Session of the American College of Cardiology New Orleans, LA, USA March 07-10, 2004; 20040307
SPONSOR: American College of Cardiology
ISSN: 0735-1097 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014469191 BIOSIS NO.: 200300424035
Additive protection of the ischemic heart ex vivo by combined treatment with delta-protein kinase C inhibitor and epsilon-protein kinase C activator.
AUTHOR: Inagaki Koichi; Hahn Harvey S; Dorn Gerald W; %%%Mochly-Rosen%%% %%% Daria%%% (Reprint
AUTHOR ADDRESS: Department of Molecular Pharmacology, Stanford University School of Medicine, 269 Campus Dr, CCSR, Room 3145A, Stanford, CA,

94305-5174, USA**USA
AUTHOR E-MAIL ADDRESS: mochly@stanford.edu
JOURNAL: Circulation 108 (7): p869-875 August 19, 2003 2003
MEDIUM: print
ISSN: 0009-7322 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Protein kinase C (PKC) plays a major role in cardioprotection from ischemia/reperfusion injury. Using an HIV-1 Tat protein-derived peptide to mediate rapid and efficient transmembrane delivery of peptide regulators of PKC translocation and function, we examined the cardioprotective effect of selective delta-PKC inhibitor (deltaV1-1) and epsilon-PKC activator (psiepsilonRACK) peptides for ischemia/reperfusion damage in isolated perfused rat hearts. Furthermore, we examined the protective effects of these PKC isozymes in isolated perfused hearts subjected to ischemia/reperfusion damage using transgenic mice expressing these peptides specifically in their cardiomyocytes. Methods and Results: In isolated perfused rat hearts, administration of deltaV1-1 but not psiepsilonRACK during reperfusion improved cardiac function and decreased creatine phosphokinase release. In contrast, pretreatment with psiepsilonRACK but not deltaV1-1, followed by a 10-minute washout before ischemia/reperfusion, also improved cardiac function and decreased creatine phosphokinase release. Furthermore, administration of psiepsilonRACK before ischemia followed by deltaV1-1 during reperfusion only conferred greater cardioprotective effects than that obtained by each peptide treatment alone. Both the delta-PKC inhibitor and epsilon-PKC activator conferred cardioprotection against ischemia/reperfusion injury in transgenic mice expressing these peptides in the heart, and coexpression of both peptides conferred greater cardioprotective effects than that obtained by the expression of each peptide alone. Conclusions: delta-PKC inhibitor prevents reperfusion injury, and epsilon-PKC activator mimics ischemic preconditioning. Furthermore, treatment with both peptides confers additive cardioprotective effects. Therefore, these peptides mediate cardioprotection by regulating ischemia/reperfusion damage at distinct time points.

13/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013718649 BIOSIS NO.: 200200312160
psiepsilonRACK, a selective PKCepsilon activating peptide, causes a positive inotropic effect in feline ventricular myocytes
AUTHOR: Harris David M (Reprint); Piacentino Valentino III (Reprint); Chaudhary Khuram (Reprint); %%%Mochly-Rosen Daria%%%; Margulies Kenneth B (Reprint); Houser Steven R (Reprint
AUTHOR ADDRESS: Temple University School of Medicine, 3400 North Broad Street, Philadelphia, PA, 19140, USA**USA
JOURNAL: Biophysical Journal 82 (1 Part 2): p70a January, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 46th Annual Meeting of the Biophysical Society San Francisco, California, USA February 23-27, 2002; 20020223
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013669752 BIOSIS NO.: 200200263263
Selective activation of epsilonPKC protects the intact heart from ischemia/reperfusion arrhythmias
AUTHOR: Restivo Mark (Reprint); Kozhevnikov Dmitry (Reprint); Qu Yongxia (Reprint); %%%Mochly-Rosen Daria%%%; Boutjdir Mohamed

AUTHOR ADDRESS: VA NY Harbor Healthcare System, Brooklyn, NY, USA**USA
JOURNAL: Circulation 104 (17 Supplement): pII.47 October 23, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001; 20011111
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013600152 BIOSIS NO.: 200200193663
Molecular %%%transporters%%% for peptides: Delivery of a cardioprotective epsilonPKC agonist peptide into cells and intact ischemic heart using a %%%transport%%% system, R7
AUTHOR: Chen Leon; Wright Lee R; Chen Che-Hong; Oliver Steven F; Wender Paul A (Reprint); %%%Mochly-Rosen Daria%%%
AUTHOR ADDRESS: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA**USA
JOURNAL: Chemistry and Biology (London) 8 (12): p1123-1129 December, 2001 2001
MEDIUM: print
ISSN: 1074-5521
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Recently, we reported a novel oligoguanidine %%%transporter%%% system, polyarginine (R7), which, when conjugated to spectroscopic probes (e.g., fluorescein) and drugs (e.g., cyclosporin A), results in highly water-soluble conjugates that rapidly enter cells and tissues. We report herein the preparation of the first R7 peptide conjugates and a study of their cellular and organ uptake and functional activity. The octapeptide psiepsilonRACK was selected for this study as it is known to exhibit selective epsilon protein kinase C isozyme agonist activity and to reduce ischemia-induced damage in cardiomyocytes. However, psiepsilonRACK is not cell-permeable. Results: Here we show that an R7-psiepsilonRACK conjugate readily enters cardiomyocytes, significantly outperforming psiepsilonRACK conjugates of the %%%transporters%%% derived from HIV Tat and from Antennapedia. Moreover, R7-psiepsilonRACK conjugate reduced ischemic damage when delivered into intact hearts either prior to or after the ischemic insult. Conclusions: Our data suggest that R7 converts a peptide lead into a potential therapeutic agent for the ischemic heart.

13/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012863703 BIOSIS NO.: 200100035542
Distortion of cardiomyocyte ultrastructure and lethal heart failure from in vivo PKC delta inhibition
AUTHOR: Hahn Harvey S (Reprint); Wu Guangyu (Reprint); Jantz Tamara (Reprint); Boivin Gregory P (Reprint); Lorenz John N (Reprint); %%%Mochly-Rosen Daria%%%; Dorn Gerald W
AUTHOR ADDRESS: Univ of Cincinnati, Cincinnati, OH, USA**USA
JOURNAL: Circulation 102 (18 Supplement): pII.160 October 31, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: Abstracts from American Heart Association Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000; 20001112
SPONSOR: American Heart Association
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RECORD TYPE: Citation
LANGUAGE: English

13/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012625258 BIOSIS NO.: 200000343571
Cardiotrophic effects of protein kinase C epsilon: Analysis by in vivo modulation of PKCepsilon translocation
AUTHOR: %%%Mochly-Rosen Daria%%%; Wu Guangyu; Hahn Harvey; Osinska Hanna; Liron Tamar; Lorenz John N; Yatani Atsuko; Robbins Jeffrey; Dorn Gerald W II (Reprint
AUTHOR ADDRESS: Division of Cardiology, University of Cincinnati Medical Center, 231 Bethesda Ave, Cincinnati, OH, 45267-0542, USA**USA
JOURNAL: Circulation Research 86 (11): p1173-1179 June 9, 2000 2000
MEDIUM: print
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein kinase C (PKC) is a key mediator of many diverse physiological and pathological responses. Although little is known about the specific in vivo roles of the various cardiac PKC isozymes, activation-induced translocation of PKC is believed to be the primary determinant of isozyme-specific functions. Recently, we have identified a catalytically inactive peptide translocation inhibitor (epsilonV1) and translocation activator (psiepsilonRACK (receptors for activated C kinase)) specifically targeting PKCepsilon. Using cardiomyocyte-specific transgenic expression of these peptides, we combined loss- and gain-of-function approaches to elucidate the in vivo consequences of myocardial PKCepsilon signaling. As expected for a PKCepsilon %%%RACK%%% binding peptide, confocal microscopy showed that epsilonV1 decorated cross-striated elements and intercalated disks of cardiac myocytes. Inhibition of cardiomyocyte PKCepsilon by epsilonV1 at lower expression levels upregulated alpha-skeletal actin gene expression, increased cardiomyocyte cell size, and modestly impaired left ventricular fractional shortening. At high expression levels, epsilonV1 caused a lethal dilated cardiomyopathy. In contrast, enhancement of PKCepsilon translocation with psiepsilonRACK resulted in selectively increased beta myosin heavy chain gene expression and normally functioning concentric ventricular remodeling with decreased cardiomyocyte size. These results identify for the first time a role for PKCepsilon signaling in normal postnatal maturational myocardial development and suggest the potential for PKCepsilon activators to stimulate "physiological" cardiomyocyte growth.

13/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012305935 BIOSIS NO.: 200000024248
Attenuation of cardiac growth in transgenic mice expressing the PKCepsilon inhibitory epsilonV1 peptide
AUTHOR: Wu Guangyu (Reprint); Wang Ying (Reprint); Jantz Tamara (Reprint); Canning Amy M (Reprint); Robbins Jeffrey; %%%Mochly-Rosen Daria%%%; Dorn Gerald W II
AUTHOR ADDRESS: Univ of Cincinnati, Cincinnati, OH, USA**USA
JOURNAL: Circulation 100 (18 SUPPL.): pI.53 Nov. 2, 1999 1999
MEDIUM: print
CONFERENCE/MEETING: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999; 19991107
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012305934 BIOSIS NO.: 200000024247
Hypertrophic effects of PKCepsilon activation in transgenic mice expressing the PKCepsilon pseudo-%%%RACK%%% peptide
AUTHOR: Wu Guangyu (Reprint); Canning Amy M (Reprint); Jantz Tamara (Reprint); %%%Mochly-Rosen Daria%%%; Dorn Gerald W II
AUTHOR ADDRESS: Univ of Cincinnati, Cincinnati, OH, USA**USA
JOURNAL: Circulation 100 (18 SUPPL.): pI.53 Nov. 2, 1999 1999
MEDIUM: print
CONFERENCE/MEETING: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999; 19991107
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012293921 BIOSIS NO.: 200000012234
Protein kinase C-epsilon is responsible for the protection of preconditioning in rabbit cardiomyocytes
AUTHOR: Liu Guang S; Cohen Michael V; %%%Mochly-Rosen Daria%%%; Downey James M (Reprint
AUTHOR ADDRESS: Department of Physiology, College of Medicine, University of South Alabama, Mobile, AL, 36688-0002, USA**USA
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (10): p1937-1948 Oct., 1999 1999
MEDIUM: print
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The role of protein kinase C (PKC) in the protection of ischemic preconditioning (PC) is still controversial, partly because of the multiple isozymes of PKC and the inability to directly measure PKC activity in vivo. In this study we have used novel peptide inhibitors which correspond to part of the amino acid sequence from the isozyme-specific %%%RACK%%%-binding site on the PKC molecule. The peptides prevent binding of a specific activated PKC isozyme to its %%%RACK%%%, thus halting isozyme translocation and function. The inhibitor peptides are cross-linked to the membrane-translocating antennapedia homeodomain peptide that allows their entry into cells. The effect of inhibitors of PKC-beta, -delta, -epsilon and -eta were evaluated. Rabbit adult ventricular myocytes were obtained by enzymatic dissociation. Ischemia was simulated by centrifuging the myocytes into an oxygen-free pellet for 180 min. PC was induced by 10 min of pelleting followed by resuspension in oxygenated medium for 15 min. During simulat ed ischemia cells undergo a predictable increase in osmotic fragility as judged by determination of the number of stained cells following their incubation in hypotonic (85 mOsm) trypan blue. The percentage of cells experiencing membrane rupture, and thus cell staining, was considered to be an index of ischemic injury. PC significantly delayed the progression of osmotic fragility during simulated ischemia ($P<0.01$). The protection of PC was abolished by the peptide inhibitor of PKC-epsilon but not by the peptide inhibitors selective for PKC-beta, PKC-delta, or PKC-eta; each was applied at 100 nM. Protection could also be induced by the PKC activator oleoylacetyl glycerol, and that protection was aborted by the inhibitor selective for PKC-epsilon, but not by the inhibitor for PKC-delta. None of the above peptide treatments affected the osmotic fragility in non-PC cells during simulated ischemia. Our studies further support PKC as a critical part of the signal transduction pathway in PC and indicate that P KC-epsilon alone is responsible for the early phase of PC's protection in rabbit cardiomyocytes.

13/7/18 (Item 18 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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0011086337 BIOSIS NO.: 199799720397
Beta-COP: A COPI coatomer protein is also an epsilon protein kinase C specific %%%rack%%%
AUTHOR: Csukai M; Chen C-H; %%%Mochly-Rosen D%%%
AUTHOR ADDRESS: Stanford Univ. Medical Sch., Stanford, CA 94305, USA**USA
JOURNAL: FASEB Journal 11 (9): pA1187 1997 1997
CONFERENCE/MEETING: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997; 19970824
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0008428761 BIOSIS NO.: 199294130602
P65 FRAGMENTS HOMOLOGOUS TO THE C2 REGION OF PROTEIN KINASE C BIND TO THE INTRACELLULAR RECEPTORS FOR PROTEIN KINASE C
AUTHOR: %%%MOCHLY-ROSEN D%%% (Reprint); MILLER K G; SCHELLER R H; KHANER H; LOPEZ J; SMITH B L
AUTHOR ADDRESS: ERNEST GALLO CLIN RES CENT, BUILDING 1, ROOM 101, SAN FRANCISCO GENERAL HOSP, SAN FRANCISCO, CALIF 94110, USA**USA
JOURNAL: Biochemistry 31 (35): p8120-8124 1992
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Receptors for activated protein kinase C (RACKs) have been isolated from the particulate cell fraction of heart and brain. We previously demonstrated that binding of protein kinase C (PKC) to RACKs requires PKC activators and is via a site on PKC that is distinct from the substrate binding site. Here, we examine the possibility that the C2 region in the regulatory domain of PKC is involved in binding of PKC to RACKs. The synaptic vesicle-specific p65 protein contains two regions homologous to the C2 region of PKC. We found that three p65 fragments, containing either one or two of these PKC C2 homologous regions, bound to highly purified RACKs. Binding of the p65 fragments and PKC to RACKs was mutually exclusive; preincubation of RACKs with the p65 fragments inhibited PKC binding, and preincubation of RACKs with PKC inhibited binding of the p65 fragments. Preincubation of the p65 fragments with a peptide resembling the PKC binding site on RACKs also inhibited p65 binding to RACKs, suggesting that PKC and p65 bind to the same or nearby regions on RACKs. Since the only homologous region between PKC and the p65 fragments is the C2 region, these results suggest that the C2 region on PKC contains at least part of the %%%RACK%%% binding site.
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